



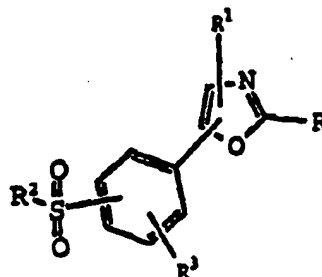
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 263/32, A61K 31/42, C07D 413/06, 413/10, 263/34, 263/38, 263/46, 263/48, C07F 9/653		A1	(11) International Publication Number: WO 96/36617 (43) International Publication Date: 21 November 1996 (21.11.96)
(21) International Application Number: PCT/US96/06992 (22) International Filing Date: 16 May 1996 (16.05.96) (30) Priority Data: 08/445,312 19 May 1995 (19.05.95) US (60) Parent Application or Grant (63) Related by Continuation US 08/445,312 (CIP) Filed on 19 May 1995 (19.05.95) (71) Applicant (for all designated States except US): G.D. SEARLE & CO. [US/US]; Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): TALLEY, John, J. [US/US]; 8772 Pine Avenue, Brentwood, MO 63144 (US). BERTENSHAW, Stephen [US/US]; 8758 Pine Avenue, Brentwood, MO 63144 (US). ROGIER, Donald, J., Jr. [US/US]; 1828 Westmeade Drive, Chesterfield, MO 63017 (US). GRANETO, Matthew [US/US]; 1510 Voltaire Drive, St. Louis, MO 63146 (US). BROWN,		David, L. [US/US]; 15504 Twingate, Chesterfield, MO 63017 (US). DEVADAS, Balekudru [IN/US]; 2175 Parasol Drive, Chesterfield, MO 63017 (US). HWANG-FUN, Lu [CN/US]; 1723 Rosslaire Court, Ballwin, MO 63021 (US). SIKORSKI, James, A. [US/US]; 2313 East Royal Court, Des Peres, MO 63131 (US). (74) Agents: BULOCK, Joseph, W. et al.; G.D. Searle & Co., Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680- 5110 (US). (81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
		Published With international search report.	

(54) Title: SUBSTITUTED OXAZOLES FOR THE TREATMENT OF INFLAMMATION

(57) Abstract

A class of substituted oxazoles is described for use in treating inflammation and inflammation-related disorders. Compounds of particular interest are defined by formula (I), wherein R is selected from hydrido, halo, mercapto, hydroxyl, carboxyalkylthio, carboxyalkylthioalkyl, carboxyalkoxy, carboxyalkoxyalkyl, haloalkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkoxy, aryloxy, aralkoxy, alkylamino, aminocarbonyl, alkoxyalkyl, carboxy(haloalkyl), alkyl, hydroxyalkyl, haloalkyl, alkenyl, hydroxyalkenyl, alkynyl, hydroxyalkynyl, cycloalkyl, cycloalkylalkyl, aminoalkyl, hydroxyalkoxyalkyl, alkylcarbonyl, phosphonylalkyl, amino acid residue, heterocyclylalkyl, cyanoalkyl, alkoxy carbonyl, alkoxy carbonylalkyl, carboxy, carboxyalkyl, arylthioalkyl, aminocarbonylalkyl, alkylcarbonylaminoalkyl, alkoxy carbonylaminoalkyl, aralkoxy carbonylaminoalkyl, aryl, heteroaryl, aralkyl, aryloxyalkyl, aralkoxyalkyl, heteroaryloxyalkyl and heteroarylalkoxyalkyl; wherein R¹ is selected from cycloalkyl, cycloalkenyl, aryl and heterocyclyl, wherein R¹ is optionally substituted at a substitutable position by alkyl, alkylamino, alkoxy and halo; wherein R² is selected from alkyl and amino; and wherein R³ is selected from hydrido and alkyl.



(I)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

SUBSTITUTED OXAZOLES FOR THE TREATMENT OF INFLAMMATION

FIELD OF THE INVENTION

5 This invention is in the field of anti-inflammatory
pharmaceutical agents and specifically relates to
compounds, compositions and methods for treating
inflammation and inflammation-associated disorders, such as
arthritis.

10

BACKGROUND OF THE INVENTION

Prostaglandins play a major role in the inflammation
process and the inhibition of prostaglandin production,
especially production of PGG₂, PGH₂ and PGE₂, has been a
15 common target of antiinflammatory drug discovery. However,
common non-steroidal antiinflammatory drugs (NSAIDs) that
are active in reducing the prostaglandin-induced pain and
swelling associated with the inflammation process are also
active in affecting other prostaglandin-regulated processes
20 not associated with the inflammation process. Thus, use of
high doses of most common NSAIDs can produce severe side
effects, including life threatening ulcers, that limit
their therapeutic potential. An alternative to NSAIDs is
the use of corticosteroids, which have even more drastic
25 side effects, especially when long term therapy is
involved.

Previous NSAIDs have been found to prevent the
production of prostaglandins by inhibiting enzymes in the
human arachidonic acid/prostaglandin pathway, including the
30 enzyme cyclooxygenase (COX). The recent discovery of an
inducible enzyme associated with inflammation (named
"cyclooxygenase-2 (COX-2)" or "prostaglandin G/H synthase
II") provides a viable target of inhibition which more
effectively reduces inflammation and produces fewer and
35 less drastic side effects.

The references below that disclose antiinflammatory
activity, show continuing efforts to find a safe and
effective antiinflammatory agent. The novel oxazoles

disclosed herein are such safe and also effective antiinflammatory agents furthering such efforts. The invention compounds are found to show usefulness in vivo as antiinflammatory agents with minimal side effects. The substituted oxazoles disclosed herein preferably selectively inhibit cyclooxygenase-2 over cyclooxygenase-1.

2,3-Diaryl-5-halo thiophenes are described in U.S. Patent No. 4,590,205 as analgesic or antiinflammatory agents. More particularly, 2,3-diaryl-5-bromo thiophenes are described in U.S. Patent No. 4,820,827 as having antiinflammatory and prostaglandin synthetase inhibitory activity for use in the treatment of inflammation and dysmenorrhea. PCT publication WO94/15932 describes 4,5-substitutedphenyl-thiophenes/furans and pyrroles as having antiinflammatory activity.

Pyrazole derivatives having antiinflammatory activity are described in U.S. Patent No. 5, 134,142, to Matsuo et al.

U.S. Patent No. 3,578,671, to K. Brown, describes antiinflammatory 4,5-diphenyloxazoles substituted in the 2-position by a saturated or unsaturated aliphatic acid. U.S. Patent No. 4,051,250, to J. Dahm et al, describes oxazole, imidazole and thiazole compounds, including 2-mercapto-4-(4-methylmercaptophenyl)-5-(4-chlorophenyl)oxazole, as having antiphlogistic, analgesic and antipyretic activity. Other related diphenyloxazole disclosures include U.S. Patent No. 4,001,228, to G. Mattalia, for antiaggregating activity and U.S. Patent No. 3,895,024, to R. Hafeli, for intermediates in the production of antiinflammatory agents. U. S. Patent No. 4,489,084, to F. Haviv and F.Kerdesky, describes diphenyloxazolyl hydrazinoalkyl nitrile compounds for use as antiinflammatory agents. U.S. Patent No. 4,143,047, to R. Harrison, describes oxazole compounds as reactants to make 2-acylamino oxazole derivatives having anti-allergy activity.

U.S. Patent No. 4,791,124, to Lutomski et al, describes the pesticide activity of substituted bis(4-halophenyl)oxazoles. U.S. Patent No. 4,775,687, to Meguro et al describes the possible use of 4,5-phenyl oxazoles as starting materials for antidiabetic compounds. WO publication No. WO92/21665, published December 9, 1992, describes bis(halophenyl)oxazole derivatives as starting materials for the preparation of antiinflammatory agents.

5 N. Meanwell et al [*J. Med. Chem.*, **35**, 3498 (1992)] describe bis(substitutedphenyl)oxazoles as having ADP-induced platelet aggregation inhibition activity.

U.S. Patent No. 4,812,470, to N. Rogers et al, describes phenyl substituted oxazoles as having antibacterial activity.

15 U.S. Patent No. 3,901,908, to K. Fitz and R. Pfister, describes 2-alkyl and 2-cycloalkyl-4,5-phenyloxazoles as intermediates in the synthesis of imidazoles having analgesic and antipyretic activity. Specifically, 2-tert-butyl-4-(4-methylsulfonylphenyl)-5-phenyloxazole is described.

20 U.S. Patent No. 4,632,930, to Carini et al, describes antihypertensive alkyl and aryl substituted imidazole, thiazole and oxazole derivatives. Specifically, 5-phenyl-4-(4-methylsulfonylphenyl)- $\alpha\alpha$ -bis(trifluoromethyl)thiazole-2-methanol is described.

25 R. Cremylin et al describe the synthesis of heterocyclic sulfonyl derivatives and specifically, 4',4''-(2-methyl-4,5-oxazoldiyl)-bis-benzenesulfonamide (*J. Heterocycl. Chem.*, **22**, 1211 (1985)).

30 T. van Es and O.G. Backeberg [*J. Chem. Soc.*, 1363 (1963)] describe the synthesis of 2-methyl-4,5-substitutedphenyloxazoles, and specifically, 4-[5-(4-chlorophenyl)-2-methyl-4-oxazolyl]benzenesulfonamide.

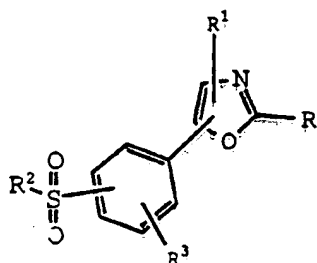
35 U.S. Patent No. 5,380,738, to Norman et al, describes 4-methylsulfonylphenyloxazoles for the treatment of inflammation. WO94//27980, published Dec. 8, 1994, describes substituted oxazoles for the treatment of

inflammation. WO95/00501, published Jan 5, 1995, describes substituted oxazoles for the treatment of inflammation.

DESCRIPTION OF THE INVENTION

5

A class of substituted oxazolyl compounds useful in treating inflammation-related disorders is defined by Formula I:



I

10

wherein R is selected from hydrido, halo, mercapto, hydroxyl, carboxyalkylthio, carboxyalkylthioalkyl, carboxyalkoxy, carboxyalkoxyalkyl, haloalkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkoxy, aryloxy, aralkoxy, alkylamino, aminocarbonyl, alkoxyalkyl, carboxy(haloalkyl), alkyl, hydroxyalkyl, haloalkyl, alkenyl, hydroxyalkenyl, alkynyl, hydroxyalkynyl, cycloalkyl, cycloalkylalkyl, aminoalkyl, hydroxyalkoxyalkyl, alkylcarbonyl, phosphonylalkyl, amino acid residue, heterocyclalkyl, cyanoalkyl, alkoxyalkyl, alkoxyalkylalkyl, carboxy, carboxyalkyl, arylthioalkyl, aminocarbonylalkyl, alkylcarbonylaminoalkyl, alkoxyalkylaminoalkyl, aralkoxyalkylaminoalkyl, aryl, heteroaryl, aralkyl, aryloxyalkyl, aralkoxyalkyl, heteroaryloxyalkyl and heteroarylalkoxyalkyl;

wherein R¹ is selected from cycloalkyl, cycloalkenyl, aryl and heterocyclalkyl, wherein R¹ is optionally substituted at a substitutable position by alkyl, alkylamino, alkoxy and halo;

30

wherein R² is selected from alkyl and amino; and wherein R³ is selected from hydrido and alkyl;

or a pharmaceutically-acceptable salt thereof;
provided R is not methyl when R² is amino and when R¹ is
phenyl or 4-halophenyl; further provided R is haloalkyl
when R³ is alkyl; and further provided that R¹ is not
5 phenyl when R² is methyl and R is isopropyl or *tert*-butyl.

The phrase "further provided", as used in the above
description, is intended to mean that the denoted proviso
is not to be considered conjunctive with the other
provisos.

10 Compounds of Formula I would be useful for, but not
limited to, the treatment of inflammation in a subject, and
for treatment of other inflammation-associated disorders,
such as, as an analgesic in the treatment of pain and
headaches, or as an antipyretic for the treatment of fever.
15 For example, compounds of the invention would be useful to
treat arthritis, including but not limited to rheumatoid
arthritis, spondyloarthropathies, gouty arthritis,
osteoarthritis, systemic lupus erythematosus and juvenile
arthritis. Such compounds of the invention would be useful
20 in the treatment of asthma, bronchitis, menstrual cramps,
tendinitis, lursitis, and skin-related conditions such as
psoriasis, eczema, burns and dermatitis. Compounds of the
invention also would be useful to treat gastrointestinal
conditions such as inflammatory bowel disease, Crohn's
25 disease, gastritis, irritable bowel syndrome and ulcerative
colitis, and for the prevention or treatment of cancer,
such as colorectal cancer. Compounds of the invention would
be useful in treating inflammation in such diseases as
vascular diseases, migraine headaches, periarteritis
30 nodosa, thyroiditis, aplastic anemia, Hodgkin's disease,
sclerodoma, rheumatic fever, type I diabetes, neuromuscular
junction disease including myasthenia gravis, white matter
disease including multiple sclerosis, sarcoidosis,
nephrotic syndrome, Behcet's syndrome, polymyositis,
35 gingivitis, nephritis, hypersensitivity, swelling occurring
after injury, myocardial ischemia, and the like. The
compounds would also be useful in the treatment of

ophthalmic diseases such as retinitis, retinopathies, uveitis, conjunctivitis, and of acute injury to the eye tissue. The compounds would also be useful in the treatment of pulmonary inflammation, such as that
5 associated with viral infections and cystic fibrosis. The compounds would also be useful for the treatment of certain central nervous system disorders such as cortical dementias including Alzheimers disease. The compounds of the invention are useful as anti-inflammatory agents, such as
10 for the treatment of arthritis, with the additional benefit of having significantly less harmful side effects. These compounds would also be useful in the treatment of allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, atherosclerosis and central nervous system damage
15 resulting from stroke, ischemia and trauma.

Besides being useful for human treatment, these compounds are also useful for veterinary treatment of mammals, including companion animals and farm animals, such as, but not limited to, horses, dogs, cats, cows, sheep and
20 pigs.

The present compounds may also be used in co-therapies, partially or completely, in place of other conventional antiinflammatories, such as together with steroids, NSAIDs, 5-lipoxygenase inhibitors, LTB₄ receptor
25 antagonists and LTA₄ hydrolase inhibitors.

Suitable LTB₄ receptor antagonists include, among others, ebselen, Bayer Bay-x-1005, Ciba Geigy compound CGS-25019C, Leo Denmark compound ETH-615, Lilly compound LY-293111, Ono compound ONO-4057, Terumo compound TMK-688,
30 Lilly compounds LY-213024, 264086 and 292728, ONO compound ONO-LB457, Searle compound SC-53228, calcitrol, Lilly compounds LY-210073, LY223982, LY233469, and LY255283, ONO compound ONO-LB-448, Searle compounds SC-41930, SC-50605 and SC-51146, and SK&F compound SKF-104493. Preferably, the
35 LTB₄ receptor antagonists are selected from ebselen, Bayer Bay-x-1005, Ciba Geigy compound CGS-25019C, Leo Denmark

compound ETH-615, Lilly compound LY-293111, Ono compound ONO-4057, and Terumo compound TMK-688.

The phrase "combination therapy" (or "co-therapy"), in defining use of a cyclooxygenase-2 inhibitor agent and
5 another agent, is intended to embrace administration of each agent in a sequential manner in a regimen that will provide beneficial effects of the drug combination, and is intended as well to embrace co-administration of these
10 agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of these active agents or in multiple, separate capsules for each agent.

Suitable 5-LO inhibitors include, among others, masoprocil, tenidap, zileuton, pranlukast, tepoxalin, rilopirox, flezelastine hydrochloride, enazadrem phosphate,
15 and bunaprolast.

The present invention preferably includes compounds which selectively inhibit cyclooxygenase-2 over cyclooxygenase-1. Preferably, the compounds have a cyclooxygenase-2 IC_{50} of less than about 0.5 μM , and also
20 have a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 50, and more preferably of at least 100. Even more preferably, the compounds have a cyclooxygenase-1 IC_{50} of greater than about 1 μM , and more preferably of greater than 20 μM .
25 Such preferred selectivity may indicate an ability to reduce the incidence of common NSAID-induced side effects.

A preferred class of compounds consists of those compounds of Formula I wherein R is selected from hydrido, halo, mercapto, hydroxyl, lower carboxyalkylthio, lower
30 carboxyalkylthioalkyl, lower carboxyalkoxy, lower carboxyalkoxyalkyl, lower haloalkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, lower alkoxy, aryloxy, lower aralkoxy, lower alkylamino, aminocarbonyl, lower alkoxyalkyl, lower carboxy(haloalkyl), lower alkyl,
35 lower hydroxyalkyl, lower haloalkyl, lower alkenyl, lower hydroxyalkenyl, lower alkynyl, lower hydroxyalkynyl, lower cycloalkyl, lower cycloalkylalkyl, lower aminoalkyl, lower

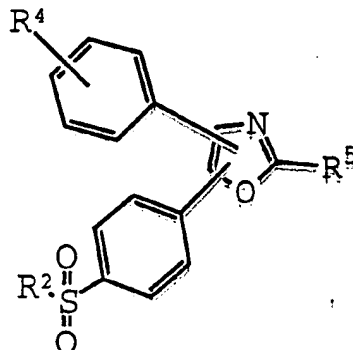
- hydroxyalkoxyalkyl, lower alkylcarbonyl, lower phosphonylalkyl, amino acid residue, lower cyanoalkyl, lower alkoxy carbonyl, lower alkoxy carbonylalkyl, carboxy, lower carboxyalkyl, lower arylthioalkyl, lower
- 5 aminocarbonylalkyl, lower alkylcarbonylaminoalkyl, lower alkoxy carbonylaminoalkyl, lower aralkoxy carbonylaminoalkyl, aryl optionally substituted at a substitutable position by carboxy, lower carboxyalkyl, lower alkyl, lower alkoxy and halo, heteroaryl optionally substituted at a substitutable
- 10 position by carboxy, lower carboxyalkyl, lower alkyl, lower alkoxy and halo, lower aralkyl optionally substituted at a substitutable position on the aryl radical by carboxy, lower carboxyalkyl, lower alkyl, lower alkoxy and halo, lower heterocyclylalkyl optionally substituted at a
- 15 substitutable position on the heterocyclyl radical by carboxy, lower carboxyalkyl, lower alkyl, lower alkoxy and halo, lower aryloxyalkyl optionally substituted at a substitutable position with halo, carboxy, lower carboxyalkyl, lower alkyl and lower alkoxy, aralkoxyalkyl
- 20 optionally substituted at a substitutable position with halo, carboxy, lower carboxyalkyl, lower alkyl and lower alkoxy, heteroarylalkoxyalkyl optionally substituted at a substitutable position with halo, carboxy, lower carboxyalkyl, lower alkyl and lower alkoxy, and
- 25 heteroaryloxyalkyl optionally substituted at a substitutable position with halo, carboxy, lower carboxyalkyl, lower alkyl and lower alkoxy; wherein R^1 is selected from lower cycloalkyl, lower cycloalkenyl, aryl and heteroaryl, wherein R^1 is optionally substituted at a
- 30 substitutable position by lower alkyl, lower alkylamino, lower alkoxy and halo; wherein R^2 is selected from lower alkyl and amino; and wherein R^3 is selected from hydrido and lower alkyl; or a pharmaceutically-acceptable salt thereof.
- 35 A class of compounds of particular interest consists of those compounds of Formula I wherein R is selected from hydrido, chloro, fluoro, bromo, iodo, mercapto, hydroxyl,

carboxymethylthio, carboxyethylthio, trifluoromethoxy, methylthio, ethylthio, methylsulfinyl, methylsulfonyl, methoxy, ethoxy, propoxy, butoxy, phenoxy, benzyloxy, N-methylamino, N,N-dimethylamino, N,N-diethylamino, aminocarbonyl, methoxymethyl, α -bromo-carboxymethyl, methyl, ethyl, n-propyl, isopropyl, butyl, tert-butyl, isobutyl, hydroxymethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, hydroxyethenyl, hydroxypropenyl, ethynyl, 1-propynyl, 2-propynyl, 1-butyne, 2-butyne, 3-butyne, hydroxyethynyl, hydroxypropynyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cyclohexylethyl, cyclohexylpropyl, cycloheptylmethyl, aminoethyl, aminopropyl, bis(hydroxymethyl)methoxymethyl, methylcarbonyl, N-benzyloxycarbonylaminomethyl, N-methoxycarbonylaminomethyl, N-methoxycarbonylaminoethyl, cyanopentyl, phenyl optionally substituted at a substitutable position by fluoro, chloro, bromo, iodo, carboxy, carboxymethyl, methyl, ethyl, n-propyl, isopropyl, butyl, tert-butyl, isobutyl, methoxy, ethoxy, propoxy and butoxy, heteroaryl selected from pyridyl, thienyl, thiazolyl, oxazolyl, imidazolyl, pyrrolyl, furyl and quinolyl, optionally substituted at a substitutable position by fluoro, chloro, bromo, iodo, carboxy, carboxymethyl, methyl, ethyl, n-propyl, isopropyl, butyl, tert-butyl, isobutyl, methoxy, ethoxy, propoxy and butoxy, lower alkyl selected from benzyl, phenethyl, diphenylmethyl and phenylpropyl, optionally substituted at a substitutable position on the phenyl radical by fluoro, chloro, bromo, iodo, carboxy, carboxymethyl, methyl, ethyl, n-propyl, isopropyl, butyl, tert-butyl, isobutyl, methoxy, ethoxy, propoxy and butoxy, lower heterocyclalkyl selected from pyrrolidinylmethyl,

pyrrolidinylethyl, pyrrolylpropyl, pyrrolylethyl, (2-methylimidazolyl)propynylphenylmethyl, piperidinylethyl, and tetrazolylpentyl, optionally substituted at a substitutable position by fluoro, chloro, bromo, iodo, carboxy, carboxymethyl, methyl, ethyl, n-propyl, isopropyl, butyl, tert-butyl, isobutyl, methoxy, ethoxy, propoxy and butoxy, phenoxymethyl optionally substituted at a substitutable position on the phenyl radical with fluoro, chloro, bromo, iodo, carboxy, carboxymethyl, methyl, ethyl, n-propyl, isopropyl, butyl, tert-butyl, isobutyl, methoxy, ethoxy, propoxy and butoxy, benzyloxymethyl optionally substituted at a substitutable position on the phenyl radical with fluoro, chloro, bromo, iodo, carboxy, carboxymethyl, methyl, ethyl, n-propyl, isopropyl, butyl, tert-butyl, isobutyl, methoxy, ethoxy, propoxy and butoxy, heteroaryloxyalkyl selected from pyridyloxymethyl and quinolyloxymethyl, optionally substituted at a substitutable position with fluoro, chloro, bromo, iodo, carboxy, carboxymethyl, methyl, ethyl, n-propyl, isopropyl, butyl, tert-butyl, isobutyl, methoxy, ethoxy, propoxy and butoxy, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, methoxycarbonylmethyl, ethoxycarbonylmethyl, methoxycarbonylethyl, ethoxycarbonylethyl, carboxy, carboxymethyl, carboxyethyl, carboxypropyl, carboxypentyl, carboxybutyl, phenylthiomethyl, aminocarbonylmethyl, N-methylaminocarbonylmethyl and N,N-dimethylaminocarbonylmethyl; wherein R¹ is selected from cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, cyclopentenyl, cycloheptenyl, phenyl, naphthyl, pyridyl, thienyl, thiazolyl, oxazolyl, imidazolyl, furyl, quinolyl, benzothiazolyl, 2,3-thianaphthalenyl, 2,3-dihydrothianaphthalenyl, 2,3-benzofuryl, and 2,3-dihydrobenzofuryl, wherein R¹ is optionally substituted at a substitutable position by methyl, ethyl, n-propyl, isopropyl, butyl, tert-butyl, isobutyl, amino, methoxy,

ethoxy, propoxy, butoxy, N-methylamino, N,N-dimethylamino, fluoro, chloro, bromo and iodo; wherein R^2 is selected from methyl, and amino; wherein R^3 is selected from hydrido, and methyl.

- 5 Within Formula I there is a subclass of compounds of high interest represented by Formula II:



II

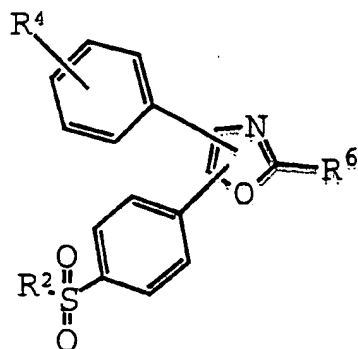
- 10 wherein R^2 is selected from lower alkyl and amino; wherein R^4 is selected from hydrido, alkyl, alkylamino, alkoxy and halo; and wherein R^5 is selected from halo, mercapto, carboxyalkylthio, carboxyalkylthioalkyl, carboxyalkoxy, carboxyalkoxyalkyl, haloalkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkoxy, aryloxy, alkylamino, aminocarbonyl, alkoxyalkyl, carboxy(haloalkyl), aminoalkyl, hydroxyalkoxyalkyl, alkylcarbonyl, phosphonylalkyl, alkylcarbonylaminoalkyl, aralkoxycarbonylaminoalkyl, amino acid residue, heterocyclylalkyl, and cyanoalkyl; or a
15
20 pharmaceutically-acceptable salt thereof.

- A preferred class of compounds consists of those compounds of Formula II wherein R^2 is selected from lower alkyl and amino; wherein R^4 is selected from hydrido, lower alkyl, lower alkylamino, lower alkoxy and halo; and wherein
25 R^5 is selected from halo, mercapto, lower carboxyalkylthio, lower carboxyalkylthioalkyl, lower haloalkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, lower alkoxy, aryloxy, lower alkylamino, aminocarbonyl, lower alkoxyalkyl, lower carboxy(haloalkyl), lower aminoalkyl, lower hydroxyalkoxyalkyl, lower alkylcarbonyl, lower
30

phosphonylalkyl, lower alkylcarbonylaminoalkyl, lower aralkoxycarbonylaminoalkyl, amino acid residue, lower heterocyclalkyl, and lower cyanoalkyl; or a pharmaceutically-acceptable salt thereof.

- 5 A class of compounds of particular interest consists of those compounds of Formula II wherein R² is selected from methyl and amino; wherein R⁴ is selected from hydrido, methyl, ethyl, n-propyl, isopropyl, butyl, tert-butyl, isobutyl, amino, methoxy, ethoxy, propoxy, butoxy, N-methylamino, N,N-dimethylamino, fluoro, chloro, bromo and iodo; and wherein R⁵ is selected from
- 10 chloro, fluoro, bromo, iodo, mercapto, carboxymethylthio, carboxyethylthio, carboxyethylthiomethyl, trifluoromethoxy, methylthio, ethylthio, methylsulfinyl, methylsulfonyl, methoxy, ethoxy, propoxy, butoxy, phenyloxy, benzyloxy, N-methylamino, N,N-dimethylamino, N,N-diethylamino, aminocarbonyl, methoxymethyl, α -bromo-carboxymethyl, aminoethyl, bis(hydroxymethyl)methoxymethyl,
- 15 methylcarbonyl, N-methylcarbonylaminomethyl, aminopropyl, pyrrolidinylmethyl, pyrrolidinylethyl, pyrrolylpropyl, pyrrolylethyl, methylcarbonylaminomethyl, N-(benzyloxycarbonyl)aminomethyl, N-(benzyloxycarbonyl)aminoethyl, N-(benzyloxycarbonyl)aminopropyl, N-methyl-N-(benzyloxycarbonyl)aminoethyl, [N-(phenylmethoxycarbonyl)amino]methoxycarbonylpropyl, [N-(phenylmethoxycarbonyl)amino]carboxypropyl,
- 20 methylcarbonyl, N-methylcarbonylaminomethyl, aminopropyl, pyrrolidinylmethyl, pyrrolidinylethyl, pyrrolylpropyl, pyrrolylethyl, methylcarbonylaminomethyl, N-(benzyloxycarbonyl)aminomethyl, N-(benzyloxycarbonyl)aminoethyl, N-(benzyloxycarbonyl)aminopropyl, N-methyl-N-(benzyloxycarbonyl)aminoethyl, [N-(phenylmethoxycarbonyl)amino]methoxycarbonylpropyl, [N-(phenylmethoxycarbonyl)amino]carboxypropyl,
- 25 (benzyloxycarbonyl)aminomethyl, N-(benzyloxycarbonyl)aminoethyl, N-(benzyloxycarbonyl)aminopropyl, N-methyl-N-(benzyloxycarbonyl)aminoethyl, [N-(phenylmethoxycarbonyl)amino]methoxycarbonylpropyl, [N-(phenylmethoxycarbonyl)amino]carboxypropyl, piperidinylethyl, tetrazolylpentyl, and cyanopentyl; or a pharmaceutically-acceptable salt thereof.
- 30

Within Formula I there is a subclass of compounds of high interest represented by Formula III

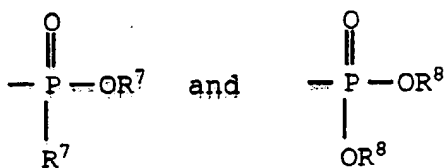


III

- wherein R^2 is selected from lower alkyl and amino;
 wherein R^4 is selected from hydrido, lower alkyl, lower
 5 alkylamino, lower alkoxy and halo; wherein R^6 is $-Y-Q$;
 wherein Y is selected from aryl, heterocyclyl,
 alkoxyalkyl, aryloxyalkyl, alkylaryloxyalkyl,
 aralkoxyalkyl, alkylaralkoxyalkyl, aminoalkyl,
 heterocyclylalkyl, alkylheterocyclyl,
 10 alkylheterocyclylalkyl, alkylaralkyl, aralkyl,
 alkynylaralkyl, alkyl, alkylsulfonylalkyl,
 alkylthioalkyl, and alkylsulfonylaminoalkyl; and
 wherein Q is an acidic moiety selected from carboxylic
 acid, tetrazole, phosphorous-containing acids, sulfur-
 15 containing acids, and the amide, ester and salt
 derivatives of said acids; provided Y is not methyl
 when Q is $-P(O)(OH)_2$; and further provided Y is not
 methyl or ethyl when Q is carboxyl; or a
 pharmaceutically-acceptable salt thereof.
- 20 A preferred class of compounds consists of those
 compounds of Formula III wherein R^2 is selected from lower
 alkyl and amino; wherein R^4 is selected from hydrido, lower
 alkyl, lower alkoxy and halo; wherein Y is selected from
 phenyl, five and six membered heterocyclyl, lower
 25 alkoxyalkyl, lower aminoalkyl, lower heterocyclylalkyl,
 lower alkylheterocyclyl, lower alkylheterocyclylalkyl,
 lower aryloxyalkyl, lower alkylaryloxyalkyl, lower
 aralkoxyalkyl, lower alkylaralkoxyalkyl, lower
 alkylaralkyl, lower alkynylaralkyl, lower aralkyl, lower
 30 alkylsulfonylalkyl, lower alkylthioalkyl, alkyl, and lower

alkylsulfonylaminoalkyl; wherein Q is selected from carboxyl, lower alkoxy carbonyl, lower aralkoxy carbonyl, tetrazolyl,

5



10

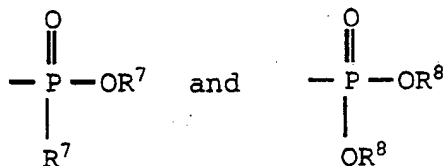
and wherein each of R⁷ and R⁸ is independently selected from hydrido, lower alkyl, lower cycloalkyl, phenyl and lower aralkyl; or a pharmaceutically-acceptable salt thereof.

15

A class of compounds of particular interest consists of those compounds of Formula III wherein R² is selected from methyl and amino; wherein R⁴ is selected from hydrido, methyl, methoxy, fluoro, chloro and bromo; wherein Y is selected from phenyl, pyridyl, pyrrolyl, pyrrolidinyl, imidazolyl, piperidinyl, methoxymethyl, 3-aminopropyl, pyrrolylmethyl, pyrrolidinylmethyl, pyrrolylpropyl, methylpyrrolyl, ethylphenylmethyl, methylphenylethyl, phenoxymethyl, methylphenoxymethyl, benzyl, ethylsulfonylmethyl, ethylthiomethyl, methylthiomethyl, methylthioethyl, methyl, ethyl, propyl, pentyl, 2,2-dimethylpropyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-methylpropyl, butyl, and methylsulfonylaminoethyl; wherein Q is selected from carboxyl, methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, benzyloxycarbonyl, tetrazolyl,

20

25



30

and wherein each of R⁷ and R⁸ is independently selected from hydrido, methyl, and ethyl; or a pharmaceutically-acceptable salt thereof.

A family of specific compounds of particular interest within Formulas I-III consists of compounds and pharmaceutically-acceptable salts thereof as follows:

- 5 4-[2-[[4-[3-(hydroxy)-1-propynyl]phenyl]methyl]-4-phenyloxazol-5-yl]benzenesulfonamide;
4-[2-[[4-[3-(N,N-dimethylamino)-1-propynyl]phenyl]methyl]-4-phenyloxazol-5-yl]benzenesulfonamide;
4-[2-[[4-[3-(N,N-dimethylamino)propyl]phenyl]methyl]-4-phenyloxazol-5-yl]benzenesulfonamide;
10 4-[2-[[4-[3-(hydroxy)-1-propynyl]phenyl]methyl]-4-phenyloxazol-5-yl]benzenesulfonamide;
1,1-dimethylethyl [3-[4-[[5-[4-(aminosulfonyl)phenyl]-4-phenyloxazol-2-yl]methyl]phenyl]-2-propynyl]carbamate;
15 4-[2-[[4-[3-(2-methyl-1H-imidazol-1-yl)-1-propyl]phenyl]methyl]-4-phenyloxazol-5-yl]benzenesulfonamide;
4-[2-[[4-[3-(amino)-1-propynyl]phenyl]methyl]-4-phenyloxazol-5-yl]benzenesulfonamide;
4-[2-[[4-[3-(tert-butylamino)-1-propynyl]phenyl]methyl]-4-phenyloxazol-5-yl]benzenesulfonamide
20 phenylmethyl [2-[5-[4-(aminosulfonyl)phenyl]-4-phenyloxazol-2-yl]methyl]carbamate;
phenylmethyl [2-[5-[4-(aminosulfonyl)phenyl]-4-phenyloxazol-2-yl]ethyl]carbamate;
25 phenylmethyl [2-[5-[4-(aminosulfonyl)phenyl]-4-phenyloxazol-2-yl]ethyl]methylcarbamate;
phenylmethyl [2-[5-[4-(aminosulfonyl)phenyl]-4-phenyloxazol-2-yl]propyl]carbamate;
methyl 5-[4-(aminosulfonyl)phenyl]- α R-
30 [[(phenylmethoxy)carbonyl]amino]-4-phenyloxazole-2-butanate;
5-[4-(aminosulfonyl)phenyl]- α R-
[[[(phenylmethoxy)carbonyl]amino]-4-phenyloxazole-2-butanate;
35 4-[4-(3-chloro-4-methoxyphenyl)-2-trifluoromethyl-5-oxazolyl]benzenesulfonamide;

- 4-phenyl-2-(benzyloxymethyl)-5-(4-methylsulfonylphenyl)oxazole;
5-phenyl-2-(benzyloxymethyl)-4-(4-methylsulfonylphenyl)oxazole;
5 [4-(3-fluoro-4-methoxyphenyl)-5-(aminosulfonylphenyl)-2-oxazolyl]methanol;
4-[5-phenyl-2-methyl-4-oxazolyl]benzenesulfonamide;
4-[5-(4-bromophenyl)-2-methyl-4-oxazolyl]benzenesulfonamide;
10 4-[5-(4-bromophenyl)-2-methoxymethyl-4-oxazolyl]benzenesulfonamide;
4-[2-methoxymethyl-5-phenyl-4-oxazolyl]benzenesulfonamide;
[5-(aminosulfonylphenyl)-4-phenyl-2-oxazolyl]-2-ethanol;
15 [5-(aminosulfonylphenyl)-4-phenyl-2-oxazolyl]-1-ethanol;
4-[4-(3-fluorophenyl)-2-methyl-5-oxazolyl]benzenesulfonamide;
4-[4-(4-chlorophenyl)-2-methoxymethyl-5-oxazolyl]benzenesulfonamide;
20 4-[4-(4-chlorophenyl)-2-methyl-5-oxazolyl]benzenesulfonamide;
[4-(phenyl)-5-(aminosulfonylphenyl)-2-oxazolyl]- α,α -dimethylmethanol;
4-[4-(4-fluorophenyl)-2-methyl-5-oxazolyl]benzenesulfonamide;
25 4-[4-(3-chlorophenyl)-2-methoxymethyl-5-oxazolyl]benzenesulfonamide;
4-[4-(3-chlorophenyl)-2-ethyl-5-oxazolyl]benzenesulfonamide;
30 [4-(3-chlorophenyl)-5-(aminosulfonylphenyl)-2-oxazolyl]-2-methanol;
[4-(4-chlorophenyl)-5-(aminosulfonylphenyl)-2-oxazolyl]-2-methanol;
4-[5-(4-chlorophenyl)-2-methoxymethyl-4-oxazolyl]benzenesulfonamide;
35 4-[5-(3-chlorophenyl)-2-methoxymethyl-4-oxazolyl]benzenesulfonamide;

- 4-[5-(3-chlorophenyl)-2-ethyl-4-oxazolyl]benzenesulfonamide;
- 4-[5-(4-fluorophenyl)-2-methoxymethyl-4-oxazolyl]benzenesulfonamide;
- 5 4-[4-phenyl-2-(1-methyl-2-pyrrolyl)-5-oxazolyl]benzenesulfonamide;
- 4-[4-phenyl-2-(methylcarbonylaminoethyl)-5-oxazolyl]benzenesulfonamide;
- 4-[5-(4-chlorophenyl)-2-methyl-4-oxazolyl]benzenesulfonamide;
- 10 4-[4-(3,4-dichlorophenyl)-2-ethyl-5-oxazolyl]benzenesulfonamide;
- [4-(3-chlorophenyl)-5-(aminosulfonylphenyl)-2-oxazolyl]- α,α -dimethylmethanol;
- 15 [5-(3-chlorophenyl)-4-(aminosulfonylphenyl)-2-oxazolyl]- α,α -dimethylmethanol;
- [4-(phenyl)-5-(aminosulfonylphenyl)-2-oxazolyl]-2-propanol;
- (R) 4-[4-phenyl-2-[2-(1-pyrrolyl)ethyl]-5-oxazolyl]benzenesulfonamide;
- 20 (S) 4-[4-phenyl-2-[2-(1-pyrrolyl)ethyl]-5-oxazolyl]benzenesulfonamide;
- 4-[4-phenyl-2-(2-pyrrolyl)-5-oxazolyl]benzenesulfonamide;
- 25 5-[(4-aminosulfonyl)phenyl]-4-phenyloxazole-2-pentanoic acid;
- methyl 5-[(4-aminosulfonyl)phenyl]-4-phenyloxazole-2-butanoate;
- 5-[(4-aminosulfonyl)phenyl]-4-phenyloxazole-2-butanoic acid;
- 30 3-[[[5-(4-aminosulfonyl)phenyl]-4-phenyloxazol-2-yl]methyl]oxy]acetic acid;
- 5-[(4-aminosulfonyl)phenyl]-4-phenyl- β,β -dimethyloxazole-2-butanoic acid;
- 35 methyl 5-[(4-aminosulfonyl)phenyl]-4-phenyloxazole-2-hexanoate;

- 5-[(4-aminosulfonyl)phenyl]-4-phenyloxazole-2-hexanoic acid;
- diethyl [[5-[(4-aminosulfonyl)phenyl]-4-phenyloxazole-2-yl]propyl]phosphonate;
- 5 [[5-[(4-aminosulfonyl)phenyl]-4-phenyloxazole-2-yl]propyl]phosphonic acid;
- diethyl [[5-[(4-aminosulfonyl)phenyl]-4-phenyloxazole-2-yl]methyl]phosphonate;
- ethyl [[5-[(4-aminosulfonyl)phenyl]-4-phenyloxazole-2-yl]methyl]phosphonate;
- 10 3-[[[5-[4-aminosulfonyl]phenyl]-4-phenyloxazol-2-yl]methyl]sulfonyl]propanoic acid;
- methyl 3-[[[5-[4-aminosulfonyl]phenyl]-4-phenyloxazol-2-yl]ethyl]thio]acetate;
- 15 3-[[[5-[4-aminosulfonyl]phenyl]-4-phenyloxazol-2-yl]ethyl]thio]acetic acid;
- tert-butyl 3-[[[5-[4-aminosulfonyl]phenyl]-4-phenyloxazol-2-yl]methyl]thio]acetate;
- 3-[[[5-[4-aminosulfonyl]phenyl]-4-phenyloxazol-2-yl]methyl]thio]acetic acid;
- 20 5-[(4-aminosulfonyl)phenyl]-4-phenyl- β -methyloxazole-2-butanoic acid;
- methyl 5-[(4-aminosulfonyl)phenyl]-4-phenyl- β -methyloxazole-2-butanoate;
- 25 4-[2-cyanopentyl-4-phenyloxazol-5-yl]benzenesulfonamide;
- 4-[(2-tetrazolyl)pentyl-4-phenyloxazol-5-yl]benzenesulfonamide;
- [[[5-[(4-aminosulfonyl)phenyl]-4-phenyloxazol-2-yl]methyl]-1-pyrrol-2-yl]carboxylic acid;
- 30 methyl [[5-[(4-aminosulfonyl)phenyl]-4-phenyloxazol-2-yl]methyl]-1-pyrrol-2-yl]carboxylate;
- [[[5-[(4-aminosulfonyl)phenyl]-4-phenyloxazol-2-yl]-2-pyrrol-1-yl]acetic acid;
- ethyl [[5-[(4-aminosulfonyl)phenyl]-4-phenyloxazol-2-yl]-2-pyrrol-1-yl]acetate;
- 35 methyl [[5-[(4-aminosulfonyl)phenyl]-4-phenyloxazol-2-yl]methyl]-1-pyrrolidin-2-yl]carboxylate;

- methyl [[5-[(4-aminosulfonyl)phenyl]-4-phenyloxazol-2-yl]propyl]aminosulfonyl]acetate;
5-[(4-aminosulfonyl)phenyl]-4-phenyl- β S-amino-oxazole-2-butanoic acid;
- 5 [5-[(4-aminosulfonyl)phenyl]-4-phenyl-oxazol-2-yl]ethyne;
4-[2-propargyl-4-phenyloxazol-5-yl]benzenesulfonamide;
[5-[(4-aminosulfonyl)phenyl]-4-phenyl-oxazol-2-yl]ethanamine;
- 10 4-[(1-piperidinyl)ethyl]-4-phenyloxazol-5-yl]benzenesulfonamide;
4-[2-(1-pyrrolidinyl)methyl]-4-phenyloxazol-5-yl]benzenesulfonamide;
4-[2-[bis(hydroxymethyl)methoxy]ethyl]-4-phenyloxazol-5-yl]benzenesulfonamide;
- 15 methyl [5-[(4-aminosulfonyl)phenyl]-4-(3,4-dichlorophenyl)oxazole]-2-propanoate;
5-[(4-aminosulfonyl)phenyl]-4-(3,4-dichlorophenyl)oxazole-2-propanoic acid;
- 20 methyl [5-[(4-aminosulfonyl)phenyl]-4-(3,4-dichlorophenyl)oxazole]-2-butanoate;
5-[(4-aminosulfonyl)phenyl]-4-(3,4-dichlorophenyl)oxazole-2-butanoic acid;
- methyl [5-[(4-aminosulfonyl)phenyl]-4-(3,4-dichlorophenyl)oxazole]-2-pentanoate;
- 25 5-[(4-aminosulfonyl)phenyl]-4-(3,4-dichlorophenyl)oxazole-2-pentanoic acid;
- 4-[(4-aminosulfonyl)phenyl]-5-(4-fluorophenyl)oxazole-2-pentanoic acid;
- 30 5-[(4-aminosulfonyl)phenyl]-4-(3,4-dichlorophenyl)- β,β -dimethyloxazole-2-butanoic acid;
4-[(4-methylsulfonyl)phenyl]-5-(3,4-dichlorophenyl)oxazole-2-butanoic acid;
- 4-[(4-aminosulfonyl)phenyl]-5-(3,4-dichlorophenyl)oxazole-2-butanoic acid;
- 35 5-[(4-aminosulfonyl)phenyl]-4-phenyl- α S-(1H-pyrrol-1-yl)oxazole-2-butanoic acid;

- 2-[5-[(4-aminosulfonyl)phenyl]-4-phenyloxazol-2-yl]ethan-2-one;
4-(2-ethenyl)-4-phenyl-oxazol-5-yl]benzenesulfonamide;
3-[[[5-[4-aminosulfonyl)phenyl]-4-phenyloxazol-2-yl)methyl]thio]propanoic acid;
5 3-[[[4-[4-aminosulfonyl)phenyl]-5-phenyloxazol-2-yl)methyl]thio]propanoic acid;
4-[2-[5-[(4-aminosulfonyl)phenyl]-4-phenyl-oxazol-2-yl)methyl]benzenepropanoic acid;
10 methyl 4-[2-[5-[(4-aminosulfonyl)phenyl]-4-phenyl-oxazol-2-yl)methyl]benzenepropynoic acid;
5-[(4-aminosulfonyl)phenyl]-4-(4-fluorophenyl)oxazole-2-pentanoic acid;
4-[2-ethyl-4-(3-fluorophenyl)oxazol-5-yl]benzenesulfonamide;
15 methyl 5-[(4-aminosulfonyl)phenyl]-4-phenyloxazole-2-pentanoate;
methyl 4-[(4-aminosulfonyl)phenyl]-5-(4-fluorophenyl)oxazole-2-pentanoate;
20 methyl 5-[(4-aminosulfonyl)phenyl]-4-(3,4-dichlorophenyl)- β,β -dimethyloxazole-2-butanoate;
methyl 4-[(4-methylsulfonyl)phenyl]-5-(3,4-dichlorophenyl)oxazole-2-butanoate;
methyl 4-[(4-aminosulfonyl)phenyl]-5-(3,4-dichlorophenyl)oxazole-2-butanoate;
25 methyl 5-[(4-aminosulfonyl)phenyl]-4-phenyl- α S-(1H-pyrrol-1-yl)oxazole-2-butanoate;
tert butyl 3-[[[5-[4-aminosulfonyl)phenyl]-4-phenyloxazol-2-yl)methyl]thio]propanoate;
30 tert butyl 3-[[[4-[4-aminosulfonyl)phenyl]-5-phenyloxazol-2-yl)methyl]thio]propanoate;
methyl 5-[(4-aminosulfonyl)phenyl]-4-(4-fluorophenyl)oxazole-2-pentanoate;
ethyl [4-(4-aminosulfonylphenyl)-5-(3-fluoro-4-methoxyphenyl)]-2-oxazoleacetate;
35 [4-(4-aminosulfonylphenyl)-5-cyclohexyl]-2-oxazoleacetic acid;

- [5-(4-aminosulfonylphenyl)-4-(4-chlorophenyl)]-2-oxazoleacetic acid;
- [4-(4-aminosulfonylphenyl)-5-(4-chlorophenyl)]-2-oxazoleacetic acid;
- 5 [4-(4-aminosulfonylphenyl)-5-(3-chloro-4-fluorophenyl)]-2-oxazoleacetic acid;
- [4-(4-aminosulfonylphenyl)-5-(3,4-dichlorophenyl)]-2-oxazoleacetic acid;
- [4-(4-aminosulfonylphenyl)-5-(3,4-difluorophenyl)]-2-oxazoleacetic acid;
- 10 [5-(3,4-difluorophenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide;
- [5-(4-aminosulfonylphenyl)-4-phenyl]-2-oxazolepropanoic acid;
- 15 4-[4-phenyl-5-oxazolyl]benzenesulfonamide;
- 4-[2-chloro-4-phenyl-5-oxazolyl]benzenesulfonamide;
- 4-[2-mercapto-4-phenyl-5-oxazolyl]benzenesulfonamide;
- 4-[2-(3-chlorophenoxy)-4-phenyl-5-oxazolyl]benzenesulfonamide;
- 20 5-(4-aminosulfonylphenyl)-4-phenyl-2-oxazolemercaptoacetic acid;
- 4-[4-phenyl-2-(2,2,2-trifluoroethoxy-5-oxazolyl]benzenesulfonamide;
- 4-[2-(methylthio)-4-phenyl-5-oxazolyl]benzenesulfonamide;
- 25 4-[2-methyl-4-phenyl-5-oxazolyl]benzenesulfonamide;
- 4-[2-methylsulfinyl]-4-phenyl-5-oxazolyl]benzenesulfonamide;
- 4-[2-(methylsulfonyl)-4-phenyl-5-oxazolyl]benzenesulfonamide;
- 30 4-[2-(2,3,4,5,6-pentafluorophenoxy)-4-phenyl-5-oxazolyl]benzenesulfonamide;
- 4-[2-methoxy-4-phenyl-5-oxazolyl]benzenesulfonamide;
- ethyl 2-[[5-(4-aminosulfonylphenyl)-4-phenyl-2-oxazolyl]oxy]benzoate;
- 35 ethyl 3-[[5-(4-aminosulfonylphenyl)-4-phenyl-2-oxazolyl]oxy]benzoate;

- 4-[2-(N,N-dimethylamino)-4-phenyl-5-oxazolyl]benzenesulfonamide;
- 4-[5-(4-chlorophenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide;
- 5 4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide;
- 4-methyl-3-[5-phenyl-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide;
- 4-[4-(3-aminosulfonyl-4-methylphenyl)-2-trifluoromethyl-5-oxazolyl]benzenesulfonamide;
- 10 4-methyl-3-[4-phenyl-2-trifluoromethyl-5-oxazolyl]benzenesulfonamide;
- 4-[4-(N,N-dimethylamino)phenyl-2-trifluoromethyl-5-oxazolyl]benzenesulfonamide;
- 15 [4-(4-aminosulfonylphenyl)-5-(3-fluoro-4-methoxyphenyl)]-2-oxazoleacetic acid;
- 4-[4-aminosulfonylphenyl)-5-(3-fluoro-4-methoxyphenyl)-2-oxazolyl]α-bromoacetic acid;
- 4-(4-methylphenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethyloxazole;
- 20 4-[5-(3-fluoro-4-methoxyphenyl)-2-methyl-4-oxazolyl]benzenesulfonamide;
- 5-(3-fluoro-4-methoxyphenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethyloxazole;
- 25 4-[5-(3-bromo-4-methoxy-5-fluorophenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide;
- [5-(4-aminosulfonylphenyl)-4-phenyl]-2-oxazolecarboxamide;
- 4-[2-methoxymethyl-4-phenyl-5-oxazolyl]benzenesulfonamide;
- 30 4-[2-benzyl-5-(phenyl)-4-oxazolyl]benzenesulfonamide;
- 4-[2-benzyl-5-(2-fluorophenyl)-4-oxazolyl]benzenesulfonamide;
- 35 4-[2-benzyl-5-(3-fluorophenyl)-4-oxazolyl]benzenesulfonamide;

- 4-[2-benzyl-5-(4-fluorophenyl)-4-oxazolyl]benzenesulfonamide;
4-[2-benzyl-5-(2,4-difluorophenyl)-4-oxazolyl]benzenesulfonamide;
5 4-[2-benzyl-5-(2,5-difluorophenyl)-4-oxazolyl]benzenesulfonamide;
4-[2-benzyl-5-(2,6-difluorophenyl)-4-oxazolyl]benzenesulfonamide;
4-[2-benzyl-5-(3,4-difluorophenyl)-4-oxazolyl]benzenesulfonamide;
10 4-[2-benzyl-5-(3,5-difluorophenyl)-4-oxazolyl]benzenesulfonamide;
4-[2-benzyl-5-(2-chlorophenyl)-4-oxazolyl]benzenesulfonamide;
15 4-[2-benzyl-5-(3-chlorophenyl)-4-oxazolyl]benzenesulfonamide;
4-[2-benzyl-5-(4-chlorophenyl)-4-oxazolyl]benzenesulfonamide;
4-[2-benzyl-5-(2,4-dichlorophenyl)-4-oxazolyl]benzenesulfonamide;
20 4-[2-benzyl-5-(2,5-dichlorophenyl)-4-oxazolyl]benzenesulfonamide;
4-[2-benzyl-5-(2,6-dichlorophenyl)-4-oxazolyl]benzenesulfonamide;
25 4-[2-benzyl-5-(3,4-dichlorophenyl)-4-oxazolyl]benzenesulfonamide;
4-[2-benzyl-5-(3,5-dichlorophenyl)-4-oxazolyl]benzenesulfonamide;
4-[2-benzyl-5-(2-methoxyphenyl)-4-oxazolyl]benzenesulfonamide;
30 4-[2-benzyl-5-(3-methoxyphenyl)-4-oxazolyl]benzenesulfonamide;
4-[2-benzyl-5-(4-methoxyphenyl)-4-oxazolyl]benzenesulfonamide;
35 4-[2-benzyl-5-(2,4-dimethoxyphenyl)-4-oxazolyl]benzenesulfonamide;

- 4-[2-benzyl-5-(2,5-dimethoxyphenyl)-4-oxazolyl]benzenesulfonamide;
4-[2-benzyl-5-(2,6-dimethoxyphenyl)-4-oxazolyl]benzenesulfonamide;
5 4-[2-benzyl-5-(3,4-dimethoxyphenyl)-4-oxazolyl]benzenesulfonamide;
4-[2-benzyl-5-(3,5-dimethoxyphenyl)-4-oxazolyl]benzenesulfonamide;
4-[2-benzyl-5-(2-methylphenyl)-4-oxazolyl]benzenesulfonamide;
10 4-[2-benzyl-5-(3-methylphenyl)-4-oxazolyl]benzenesulfonamide;
4-[2-benzyl-5-(4-methylphenyl)-4-oxazolyl]benzenesulfonamide;
15 4-[2-benzyl-5-(2,4-dimethylphenyl)-4-oxazolyl]benzenesulfonamide;
4-[2-benzyl-5-(2,5-dimethylphenyl)-4-oxazolyl]benzenesulfonamide;
4-[2-benzyl-5-(2,6-dimethylphenyl)-4-oxazolyl]benzenesulfonamide;
20 4-[2-benzyl-5-(3,4-dimethylphenyl)-4-oxazolyl]benzenesulfonamide;
4-[2-benzyl-5-(3,5-dimethylphenyl)-4-oxazolyl]benzenesulfonamide;
25 4-[2-benzyl-5-(2-chloro-4-methylphenyl)-4-oxazolyl]benzenesulfonamide;
4-[2-benzyl-5-(3-chloro-4-methylphenyl)-4-oxazolyl]benzenesulfonamide;
4-[2-benzyl-5-(3-chloro-2-methylphenyl)-4-oxazolyl]benzenesulfonamide;
30 4-[2-benzyl-5-(2-chloro-6-methylphenyl)-4-oxazolyl]benzenesulfonamide;
4-[2-benzyl-5-(4-chloro-2-methylphenyl)-4-oxazolyl]benzenesulfonamide;
35 4-[2-benzyl-5-(4-chloro-3-methylphenyl)-4-oxazolyl]benzenesulfonamide;

- 4-[2-benzyl-5-(2-chloro-4-methoxyphenyl)-4-oxazolyl]benzenesulfonamide;
- 4-[2-benzyl-5-(3-chloro-4-methoxyphenyl)-4-oxazolyl]benzenesulfonamide;
- 5 4-[2-benzyl-5-(3-chloro-2-methoxyphenyl)-4-oxazolyl]benzenesulfonamide;
- 4-[2-benzyl-5-(2-chloro-6-methoxyphenyl)-4-oxazolyl]benzenesulfonamide;
- 4-[2-benzyl-5-(4-chloro-2-methoxyphenyl)-4-oxazolyl]benzenesulfonamide;
- 10 4-[2-benzyl-5-(4-chloro-3-methoxyphenyl)-4-oxazolyl]benzenesulfonamide;
- 4-[2-benzyl-5-(3,5-dichloro-4-methoxyphenyl)-4-oxazolyl]benzenesulfonamide;
- 15 4-[2-benzyl-5-(2-fluoro-4-methylphenyl)-4-oxazolyl]benzenesulfonamide;
- 4-[2-benzyl-5-(3-fluoro-4-methylphenyl)-4-oxazolyl]benzenesulfonamide;
- 4-[2-benzyl-5-(3-fluoro-2-methylphenyl)-4-oxazolyl]benzenesulfonamide;
- 20 4-[2-benzyl-5-(2-fluoro-6-methylphenyl)-4-oxazolyl]benzenesulfonamide;
- 4-[2-benzyl-5-(4-fluoro-2-methylphenyl)-4-oxazolyl]benzenesulfonamide;
- 25 4-[2-benzyl-5-(4-fluoro-3-methylphenyl)-4-oxazolyl]benzenesulfonamide;
- 4-[2-benzyl-5-(2-fluoro-4-methoxyphenyl)-4-oxazolyl]benzenesulfonamide;
- 4-[2-benzyl-5-(3-fluoro-4-methoxyphenyl)-4-oxazolyl]benzenesulfonamide;
- 30 4-[2-benzyl-5-(3-fluoro-2-methoxyphenyl)-4-oxazolyl]benzenesulfonamide;
- 4-[2-benzyl-5-(2-fluoro-6-methoxyphenyl)-4-oxazolyl]benzenesulfonamide;
- 35 4-[2-benzyl-5-(4-fluoro-2-methoxyphenyl)-4-oxazolyl]benzenesulfonamide;

- 4-[2-benzyl-5-(2-thienyl)-4-oxazolyl]benzenesulfonamide;
4-[2-benzyl-5-(5-chloro-2-thienyl)-4-oxazolyl]benzenesulfonamide;
5 4-[2-benzyl-5-(yl)-4-oxazolyl]benzenesulfonamide;
4-[2-benzyl-5-(1-cyclohexenyl)-4-oxazolyl]benzenesulfonamide;
4-[2-benzyl-5-(2-cyclohexenyl)-4-oxazolyl]benzenesulfonamide;
10 4-[2-benzyl-5-(3-cyclohexenyl)-4-oxazolyl]benzenesulfonamide;
2-benzyl-4-(4-methylsulfonylphenyl)-5-phenyloxazole;
2-benzyl-4-(4-methylsulfonylphenyl)-5-(2-fluorophenyl) oxazole;
15 2-benzyl-4-(4-methylsulfonylphenyl)-5-(3-fluorophenyl) oxazole;
2-benzyl-4-(4-methylsulfonylphenyl)-5-(2,4-difluorophenyl) oxazole;
2-benzyl-4-(4-methylsulfonylphenyl)-5-(2,5-difluorophenyl) oxazole;
20 2-benzyl-4-(4-methylsulfonylphenyl)-5-(2,6-difluorophenyl) oxazole;
2-benzyl-4-(4-methylsulfonylphenyl)-5-(3,4-difluorophenyl) oxazole;
25 2-benzyl-4-(4-methylsulfonylphenyl)-5-(3,5-difluorophenyl) oxazole;
2-benzyl-4-(4-methylsulfonylphenyl)-5-(2-chlorophenyl) oxazole;
2-benzyl-4-(4-methylsulfonylphenyl)-5-(3-chlorophenyl) oxazole;
30 2-benzyl-4-(4-methylsulfonylphenyl)-5-(4-chlorophenyl) oxazole;
2-benzyl-4-(4-methylsulfonylphenyl)-5-(2,4-dichlorophenyl) oxazole;
35 2-benzyl-4-(4-methylsulfonylphenyl)-5-(2,5-dichlorophenyl) oxazole;

- 2-benzyl-4-(4-methylsulfonylphenyl)-5-(2,6-dichlorophenyl)oxazole;
2-benzyl-4-(4-methylsulfonylphenyl)-5-(3,4-dichlorophenyl)oxazole;
5 2-benzyl-4-(4-methylsulfonylphenyl)-5-(3,5-dichlorophenyl)oxazole;
2-benzyl-4-(4-methylsulfonylphenyl)-5-(2-methoxyphenyl)oxazole;
2-benzyl-4-(4-methylsulfonylphenyl)-5-(3-methoxyphenyl)oxazole;
10 2-benzyl-4-(4-methylsulfonylphenyl)-5-(4-methoxyphenyl)oxazole;
2-benzyl-4-(4-methylsulfonylphenyl)-5-(2,4-dimethoxyphenyl)oxazole;
15 2-benzyl-4-(4-methylsulfonylphenyl)-5-(2,5-dimethoxyphenyl)oxazole;
2-benzyl-4-(4-methylsulfonylphenyl)-5-(2,6-dimethoxyphenyl)oxazole;
2-benzyl-4-(4-methylsulfonylphenyl)-5-(3,4-dimethoxyphenyl)oxazole;
20 2-benzyl-4-(4-methylsulfonylphenyl)-5-(3,5-dimethoxyphenyl)oxazole;
2-benzyl-4-(4-methylsulfonylphenyl)-5-(2-methylphenyl)oxazole;
25 2-benzyl-4-(4-methylsulfonylphenyl)-5-(3-methylphenyl)oxazole;
2-benzyl-4-(4-methylsulfonylphenyl)-5-(4-methylphenyl)oxazole;
2-benzyl-4-(4-methylsulfonylphenyl)-5-(2,4-dimethylphenyl)oxazole;
30 2-benzyl-4-(4-methylsulfonylphenyl)-5-(2,5-dimethylphenyl)oxazole;
2-benzyl-4-(4-methylsulfonylphenyl)-5-(2,6-dimethylphenyl)oxazole;
35 2-benzyl-4-(4-methylsulfonylphenyl)-5-(3,4-dimethylphenyl)oxazole;

- 2-benzyl-4-(4-methylsulfonylphenyl)-5-(3,5-dimethylphenyl)oxazole;
- 2-benzyl-4-(4-methylsulfonylphenyl)-5-(2-chloro-4-methylphenyl)oxazole;
- 5 2-benzyl-4-(4-methylsulfonylphenyl)-5-(3-chloro-4-methylphenyl)oxazole;
- 2-benzyl-4-(4-methylsulfonylphenyl)-5-(3-chloro-2-methylphenyl)oxazole;
- 2-benzyl-4-(4-methylsulfonylphenyl)-5-(2-chloro-6-methylphenyl)oxazole;
- 10 2-benzyl-4-(4-methylsulfonylphenyl)-5-(4-chloro-2-methylphenyl)oxazole;
- 2-benzyl-4-(4-methylsulfonylphenyl)-5-(4-chloro-3-methylphenyl)oxazole;
- 15 2-benzyl-4-(4-methylsulfonylphenyl)-5-(2-chloro-4-methoxyphenyl)oxazole;
- 2-benzyl-4-(4-methylsulfonylphenyl)-5-(3-chloro-4-methoxyphenyl)oxazole;
- 2-benzyl-4-(4-methylsulfonylphenyl)-5-(3-chloro-2-methoxyphenyl)oxazole;
- 20 2-benzyl-4-(4-methylsulfonylphenyl)-5-(2-chloro-6-methoxyphenyl)oxazole;
- 2-benzyl-4-(4-methylsulfonylphenyl)-5-(4-chloro-2-methoxyphenyl)oxazole;
- 25 2-benzyl-4-(4-methylsulfonylphenyl)-5-(4-chloro-3-methoxyphenyl)oxazole;
- 2-benzyl-4-(4-methylsulfonylphenyl)-5-(3,5-dichloro-4-methoxyphenyl)oxazole;
- 2-benzyl-4-(4-methylsulfonylphenyl)-5-(2-fluoro-4-methylphenyl)oxazole;
- 30 2-benzyl-4-(4-methylsulfonylphenyl)-5-(3-fluoro-4-methylphenyl)oxazole;
- 2-benzyl-4-(4-methylsulfonylphenyl)-5-(3-fluoro-2-methylphenyl)oxazole;
- 35 2-benzyl-4-(4-methylsulfonylphenyl)-5-(2-fluoro-6-methylphenyl)oxazole;

- 2-benzyl-4-(4-methylsulfonylphenyl)-5-(4-fluoro-2-methylphenyl) oxazole;
- 2-benzyl-4-(4-methylsulfonylphenyl)-5-(4-fluoro-3-methylphenyl) oxazole;
- 5 2-benzyl-4-(4-methylsulfonylphenyl)-5-(2-fluoro-4-methoxyphenyl) oxazole;
- 2-benzyl-4-(4-methylsulfonylphenyl)-5-(3-fluoro-4-methoxyphenyl) oxazole;
- 2-benzyl-4-(4-methylsulfonylphenyl)-5-(3-fluoro-2-methoxyphenyl) oxazole;
- 10 2-benzyl-4-(4-methylsulfonylphenyl)-5-(2-fluoro-6-methoxyphenyl) oxazole;
- 2-benzyl-4-(4-methylsulfonylphenyl)-5-(4-fluoro-2-methoxyphenyl) oxazole;
- 15 2-benzyl-4-(4-methylsulfonylphenyl)-5-(2-thienyl) oxazole;
- 2-benzyl-4-(4-methylsulfonylphenyl)-5-(5-chloro-2-thienyl) oxazole;
- 2-benzyl-4-(4-methylsulfonylphenyl)-5-
- 20 (cyclohexyl) oxazole;
- 2-benzyl-4-(4-methylsulfonylphenyl)-5-(1-cyclohexenyl) oxazole;
- 2-benzyl-4-(4-methylsulfonylphenyl)-5-(2-cyclohexenyl) oxazole;
- 25 2-benzyl-4-(4-methylsulfonylphenyl)-5-(3-cyclohexenyl) oxazole;
- 2-(ethyl)-4-(4-methylsulfonylphenyl)-5-phenyloxazole;
- 2-(trifluoromethyl)-4-(4-methylsulfonylphenyl)-5-phenyloxazole;
- 30 2-(difluoromethyl)-4-(4-methylsulfonylphenyl)-5-phenyloxazole;
- 2-(hydroxymethyl)-4-(4-methylsulfonylphenyl)-5-phenyloxazole;
- 35 [4-(4-methylsulfonylphenyl)-5-phenyl]-2-oxazolecarboxylic acid;

- methyl [4-(4-methylsulfonylphenyl)-5-phenyl]-2-oxazolecarboxylate;
ethyl [4-(4-methylsulfonylphenyl)-5-phenyl]-2-oxazolecarboxylate;
- 5 2-(propyl)-4-(4-methylsulfonylphenyl)-5-phenyloxazole;
2-(benzyl)-4-(4-methylsulfonylphenyl)-5-phenyloxazole;
2-(phenylthiomethyl)-4-(4-methylsulfonylphenyl)-5-phenyloxazole;
- 10 2-(phenoxymethyl)-4-(4-methylsulfonylphenyl)-5-phenyloxazole;
2-((4-chlorophenoxy)methyl)-4-(4-methylsulfonylphenyl)-5-phenyloxazole;
- 15 2-((3-chlorophenoxy)methyl)-4-(4-methylsulfonylphenyl)-5-phenyloxazole;
2-((2-chlorophenoxy)methyl)-4-(4-methylsulfonylphenyl)-5-phenyloxazole;
2-((4-fluorophenoxy)methyl)-4-(4-methylsulfonylphenyl)-5-phenyloxazole;
- 20 2-((3-fluorophenoxy)methyl)-4-(4-methylsulfonylphenyl)-5-phenyloxazole;
2-((2-fluorophenoxy)methyl)-4-(4-methylsulfonylphenyl)-5-phenyloxazole;
- 25 2-((4-carboxyphenoxy)methyl)-4-(4-methylsulfonylphenyl)-5-phenyloxazole;
2-((3-carboxyphenoxy)methyl)-4-(4-methylsulfonylphenyl)-5-phenyloxazole;
2-((2-carboxyphenoxy)methyl)-4-(4-methylsulfonylphenyl)-5-phenyloxazole;
- 30 2-(2-phenethyl)-4-(4-methylsulfonylphenyl)-5-phenyloxazole;
2-(3-phenylpropyl)-4-(4-methylsulfonylphenyl)-5-phenyloxazole;
- 35 [4-(4-methylsulfonylphenyl)-5-phenyl]-2-oxazoleacetic acid;

- ethyl [4-(4-methylsulfonylphenyl)-5-phenyl]-2-oxazoleacetate;
methyl [4-(4-methylsulfonylphenyl)-5-phenyl]-2-oxazoleacetate;
5 [4-(4-methylsulfonylphenyl)-5-phenyl]-2-oxazolepropanoic acid;
ethyl [4-(4-methylsulfonylphenyl)-5-phenyl]-2-oxazolepropanoate;
methyl [4-(4-methylsulfonylphenyl)-5-phenyl]-2-oxazolepropanoate;
10 [4-(4-methylsulfonylphenyl)-5-phenyl]-2-oxazolebutanoic acid;
ethyl [4-(4-methylsulfonylphenyl)-5-phenyl]-2-oxazolebutanoate;
15 methyl [4-(4-methylsulfonylphenyl)-5-phenyl]-2-oxazolebutanoate;
2-(2-quinolyloxymethyl)-4-(4-methylsulfonylphenyl)-5-phenyloxazole;
4-[2-(ethyl)-5-phenyl-4-oxazolyl]benzenesulfonamide;
20 4-[2-(trifluoromethyl)-5-phenyl-4-oxazolyl]benzenesulfonamide;
4-[2-(difluoromethyl)-5-phenyl-4-oxazolyl]benzenesulfonamide;
4-[2-(hydroxymethyl)-5-phenyl-4-oxazolyl]benzenesulfonamide;
25 [4-(4-aminosulfonylphenyl)-5-phenyl]-2-oxazolecarboxylic acid;
methyl [4-(4-aminosulfonylphenyl)-5-phenyl]-2-oxazolecarboxylate;
30 ethyl [4-(4-aminosulfonylphenyl)-5-phenyl]-2-oxazolecarboxylate;
4-[2-(propyl)-5-phenyl-4-oxazolyl]benzenesulfonamide;
4-[2-(benzyl)-5-phenyl-4-oxazolyl]benzenesulfonamide;
35 4-[2-(phenylthiomethyl)-5-phenyl-4-oxazolyl]benzenesulfonamide;

- 4-[2-(phenoxyethyl)-5-phenyl-4-oxazolyl]benzenesulfonamide;
4-[2-((4-chlorophenoxy)methyl)-5-phenyl-4-oxazolyl]benzenesulfonamide;
5 4-[2-((3-chlorophenoxy)methyl)-5-phenyl-4-oxazolyl]benzenesulfonamide;
4-[2-((2-chlorophenoxy)methyl)-5-phenyl-4-oxazolyl]benzenesulfonamide;
4-[2-((4-fluorophenoxy)methyl)-5-phenyl-4-oxazolyl]benzenesulfonamide;
10 4-[2-((3-fluorophenoxy)methyl)-5-phenyl-4-oxazolyl]benzenesulfonamide;
4-[2-((2-fluorophenoxy)methyl)-5-phenyl-4-oxazolyl]benzenesulfonamide;
15 4-[2-((4-carboxyphenoxy)methyl)-5-phenyl-4-oxazolyl]benzenesulfonamide;
4-[2-((3-carboxyphenoxy)methyl)-5-phenyl-4-oxazolyl]benzenesulfonamide;
4-[2-((2-carboxyphenoxy)methyl)-5-phenyl-4-oxazolyl]benzenesulfonamide;
20 4-[2-(2-phenylethyl)-5-phenyl-4-oxazolyl]benzenesulfonamide;
4-[2-(3-phenylpropyl)-5-phenyl-4-oxazolyl]benzenesulfonamide;
25 [4-(4-aminosulfonylphenyl)-5-phenyl]-2-oxazoleacetic acid;
methyl [4-(4-aminosulfonylphenyl)-5-phenyl]-2-oxazoleacetate;
ethyl [4-(4-aminosulfonylphenyl)-5-phenyl]-2-oxazoleacetate;
30 [4-(4-aminosulfonylphenyl)-5-phenyl]-2-oxazolepropanoic acid;
methyl [4-(4-aminosulfonylphenyl)-5-phenyl]-2-oxazolepropanoate;
35 ethyl [4-(4-aminosulfonylphenyl)-5-phenyl]-2-oxazolepropanoate;

- [4-(4-aminosulfonylphenyl)-5-phenyl]-2-oxazolebutanoic acid;
methyl [4-(4-aminosulfonylphenyl)-5-phenyl]-2-oxazolebutanoate;
5 ethyl [4-(4-aminosulfonylphenyl)-5-phenyl]-2-oxazolebutanoate;
4-[2-(2-quinolyloxymethyl)-5-phenyl-4-oxazolyl]benzenesulfonamide;
4-[2-benzyl-4-phenyl-5-oxazolyl]benzenesulfonamide;
10 4-[2-benzyl-4-(2-fluorophenyl)-5-oxazolyl]benzenesulfonamide;
4-[2-benzyl-4-(3-fluorophenyl)-5-oxazolyl]benzenesulfonamide;
4-[2-benzyl-4-(4-fluorophenyl)-5-oxazolyl]benzenesulfonamide;
15 4-[2-benzyl-4-(2,4-difluorophenyl)-5-oxazolyl]benzenesulfonamide;
4-[2-benzyl-4-(2,5-difluorophenyl)-5-oxazolyl]benzenesulfonamide;
20 4-[2-benzyl-4-(2,6-difluorophenyl)-5-oxazolyl]benzenesulfonamide;
4-[2-benzyl-4-(3,4-difluorophenyl)-5-oxazolyl]benzenesulfonamide;
4-[2-benzyl-4-(3,5-difluorophenyl)-5-oxazolyl]benzenesulfonamide;
25 4-[2-benzyl-4-(2-chlorophenyl)-5-oxazolyl]benzenesulfonamide;
4-[2-benzyl-4-(3-chlorophenyl)-5-oxazolyl]benzenesulfonamide;
30 4-[2-benzyl-4-(4-chlorophenyl)-5-oxazolyl]benzenesulfonamide;
4-[2-benzyl-4-(2,4-dichlorophenyl)-5-oxazolyl]benzenesulfonamide;
4-[2-benzyl-4-(2,5-dichlorophenyl)-5-oxazolyl]benzenesulfonamide;
35 4-[2-benzyl-4-(2,6-dichlorophenyl)-5-oxazolyl]benzenesulfonamide;

- 4-[2-benzyl-4-(3,4-dichlorophenyl)-5-oxazolyl]benzenesulfonamide;
4-[2-benzyl-4-(3,5-dichlorophenyl)-5-oxazolyl]benzenesulfonamide;
5 4-[2-benzyl-4-(2-methoxyphenyl)-5-oxazolyl]benzenesulfonamide;
4-[2-benzyl-4-(3-methoxyphenyl)-5-oxazolyl]benzenesulfonamide;
4-[2-benzyl-4-(4-methoxyphenyl)-5-oxazolyl]benzenesulfonamide;
10 4-[2-benzyl-4-(2,4-dimethoxyphenyl)-5-oxazolyl]benzenesulfonamide;
4-[2-benzyl-4-(2,5-dimethoxyphenyl)-5-oxazolyl]benzenesulfonamide;
15 4-[2-benzyl-4-(2,6-dimethoxyphenyl)-5-oxazolyl]benzenesulfonamide;
4-[2-benzyl-4-(3,4-dimethoxyphenyl)-5-oxazolyl]benzenesulfonamide;
4-[2-benzyl-4-(3,5-dimethoxyphenyl)-5-oxazolyl]benzenesulfonamide;
20 4-[2-benzyl-4-(2-methylphenyl)-5-oxazolyl]benzenesulfonamide;
4-[2-benzyl-4-(3-methylphenyl)-5-oxazolyl]benzenesulfonamide;
25 4-[2-benzyl-4-(4-methylphenyl)-5-oxazolyl]benzenesulfonamide;
4-[2-benzyl-4-(2,4-dimethylphenyl)-5-oxazolyl]benzenesulfonamide;
4-[2-benzyl-4-(2,5-dimethylphenyl)-5-oxazolyl]benzenesulfonamide;
30 4-[2-benzyl-4-(2,6-dimethylphenyl)-5-oxazolyl]benzenesulfonamide;
4-[2-benzyl-4-(3,4-dimethylphenyl)-5-oxazolyl]benzenesulfonamide;
35 4-[2-benzyl-4-(3,5-dimethylphenyl)-5-oxazolyl]benzenesulfonamide;

- 4-[2-benzyl-4-(2-chloro-4-methylphenyl)-5-oxazolyl]benzenesulfonamide;
- 4-[2-benzyl-4-(3-chloro-4-methylphenyl)-5-oxazolyl]benzenesulfonamide;
- 5 4-[2-benzyl-4-(3-chloro-2-methylphenyl)-5-oxazolyl]benzenesulfonamide;
- 4-[2-benzyl-4-(2-chloro-6-methylphenyl)-5-oxazolyl]benzenesulfonamide;
- 4-[2-benzyl-4-(4-chloro-2-methylphenyl)-5-oxazolyl]benzenesulfonamide;
- 10 4-[2-benzyl-4-(4-chloro-3-methylphenyl)-5-oxazolyl]benzenesulfonamide;
- 4-[2-benzyl-4-(2-chloro-4-methoxyphenyl)-5-oxazolyl]benzenesulfonamide;
- 15 4-[2-benzyl-4-(3-chloro-4-methoxyphenyl)-5-oxazolyl]benzenesulfonamide;
- 4-[2-benzyl-4-(3-chloro-2-methoxyphenyl)-5-oxazolyl]benzenesulfonamide;
- 4-[2-benzyl-4-(2-chloro-6-methoxyphenyl)-5-oxazolyl]benzenesulfonamide;
- 20 4-[2-benzyl-4-(4-chloro-2-methoxyphenyl)-5-oxazolyl]benzenesulfonamide;
- 4-[2-benzyl-4-(4-chloro-3-methoxyphenyl)-5-oxazolyl]benzenesulfonamide;
- 25 4-[2-benzyl-4-(3,5-dichloro-4-methoxyphenyl)-5-oxazolyl]benzenesulfonamide;
- 4-[2-benzyl-4-(2-fluoro-4-methylphenyl)-5-oxazolyl]benzenesulfonamide;
- 4-[2-benzyl-4-(3-fluoro-4-methylphenyl)-5-oxazolyl]benzenesulfonamide;
- 30 4-[2-benzyl-4-(3-fluoro-2-methylphenyl)-5-oxazolyl]benzenesulfonamide;
- 4-[2-benzyl-4-(2-fluoro-6-methylphenyl)-5-oxazolyl]benzenesulfonamide;
- 35 4-[2-benzyl-4-(4-fluoro-2-methylphenyl)-5-oxazolyl]benzenesulfonamide;

- 4-[2-benzyl-4-(4-fluoro-3-methylphenyl)-5-oxazolyl]benzenesulfonamide;
4-[2-benzyl-4-(2-fluoro-4-methoxyphenyl)-5-oxazolyl]benzenesulfonamide;
5 4-[2-benzyl-4-(3-fluoro-4-methoxyphenyl)-5-oxazolyl]benzenesulfonamide;
4-[2-benzyl-4-(3-fluoro-2-methoxyphenyl)-5-oxazolyl]benzenesulfonamide;
4-[2-benzyl-4-(2-fluoro-6-methoxyphenyl)-5-oxazolyl]benzenesulfonamide;
10 4-[2-benzyl-4-(4-fluoro-2-methoxyphenyl)-5-oxazolyl]benzenesulfonamide;
4-[2-benzyl-4-(2-thienyl)-5-oxazolyl]benzenesulfonamide;
15 4-[2-benzyl-4-(5-chloro-2-thienyl)-5-oxazolyl]benzenesulfonamide;
4-[2-benzyl-4-(cyclohexyl)-5-oxazolyl]benzenesulfonamide;
4-[2-benzyl-4-(1-cyclohexenyl)-5-oxazolyl]benzenesulfonamide;
20 4-[2-benzyl-4-(2-cyclohexenyl)-5-oxazolyl]benzenesulfonamide;
4-[2-benzyl-4-(3-cyclohexenyl)-5-oxazolyl]benzenesulfonamide;
25 2-benzyl-5-(4-methylsulfonylphenyl)-4-phenyloxazole;
2-benzyl-5-(4-methylsulfonylphenyl)-4-(2-fluorophenyl)oxazole;
2-benzyl-5-(4-methylsulfonylphenyl)-4-(3-fluorophenyl)oxazole;
30 2-benzyl-5-(4-methylsulfonylphenyl)-4-(2,4-difluorophenyl)oxazole;
2-benzyl-5-(4-methylsulfonylphenyl)-4-(2,5-difluorophenyl)oxazole;
2-benzyl-5-(4-methylsulfonylphenyl)-4-(2,6-difluorophenyl)oxazole;
35 2-benzyl-5-(4-methylsulfonylphenyl)-4-(3,4-difluorophenyl)oxazole;

- 2-benzyl-5-(4-methylsulfonylphenyl)-4-(3,5-difluorophenyl)oxazole;
- 2-benzyl-5-(4-methylsulfonylphenyl)-4-(2-chlorophenyl)-4-oxazolyl]benzenesulfonamide;
- 5 2-benzyl-5-(4-methylsulfonylphenyl)-4-(3-chlorophenyl)oxazole;
- 2-benzyl-5-(4-methylsulfonylphenyl)-4-(4-chlorophenyl)-4-oxazolyl]benzenesulfonamide;
- 2-benzyl-5-(4-methylsulfonylphenyl)-4-(2,4-dichlorophenyl)oxazole;
- 10 2-benzyl-5-(4-methylsulfonylphenyl)-4-(2,5-dichlorophenyl)oxazole;
- 2-benzyl-5-(4-methylsulfonylphenyl)-4-(2,6-dichlorophenyl)oxazole;
- 15 2-benzyl-5-(4-methylsulfonylphenyl)-4-(3,4-dichlorophenyl)oxazole;
- 2-benzyl-5-(4-methylsulfonylphenyl)-4-(3,5-dichlorophenyl)oxazole;
- 2-benzyl-5-(4-methylsulfonylphenyl)-4-(2-methoxyphenyl)oxazole;
- 20 2-benzyl-5-(4-methylsulfonylphenyl)-4-(3-methoxyphenyl)oxazole;
- 2-benzyl-5-(4-methylsulfonylphenyl)-4-(4-methoxyphenyl)oxazole;
- 25 2-benzyl-5-(4-methylsulfonylphenyl)-4-(2,4-dimethoxyphenyl)oxazole;
- 2-benzyl-5-(4-methylsulfonylphenyl)-4-(2,5-dimethoxyphenyl)oxazole;
- 2-benzyl-5-(4-methylsulfonylphenyl)-4-(2,6-dimethoxyphenyl)oxazole;
- 30 2-benzyl-5-(4-methylsulfonylphenyl)-4-(3,4-dimethoxyphenyl)oxazole;
- 2-benzyl-5-(4-methylsulfonylphenyl)-4-(3,5-dimethoxyphenyl)oxazole;
- 35 2-benzyl-5-(4-methylsulfonylphenyl)-4-(2-methylphenyl)oxazole;

- 2-benzyl-5-(4-methylsulfonylphenyl)-4-(3-methylphenyl) oxazole;
- 2-benzyl-5-(4-methylsulfonylphenyl)-4-(4-methylphenyl) oxazole;
- 5 2-benzyl-5-(4-methylsulfonylphenyl)-4-(2,4-dimethylphenyl) oxazole;
- 2-benzyl-5-(4-methylsulfonylphenyl)-4-(2,5-dimethylphenyl) oxazole;
- 2-benzyl-5-(4-methylsulfonylphenyl)-4-(2,6-dimethylphenyl) oxazole;
- 10 2-benzyl-5-(4-methylsulfonylphenyl)-4-(3,4-dimethylphenyl) oxazole;
- 2-benzyl-5-(4-methylsulfonylphenyl)-4-(3,5-dimethylphenyl) oxazole;
- 15 2-benzyl-5-(4-methylsulfonylphenyl)-4-(2-chloro-4-methylphenyl) oxazole;
- 2-benzyl-5-(4-methylsulfonylphenyl)-4-(3-chloro-4-methylphenyl) oxazole;
- 2-benzyl-5-(4-methylsulfonylphenyl)-4-(3-chloro-2-methylphenyl) oxazole;
- 20 2-benzyl-5-(4-methylsulfonylphenyl)-4-(2-chloro-6-methylphenyl) oxazole;
- 2-benzyl-5-(4-methylsulfonylphenyl)-4-(4-chloro-2-methylphenyl) oxazole;
- 25 2-benzyl-5-(4-methylsulfonylphenyl)-4-(4-chloro-3-methylphenyl) oxazole;
- 2-benzyl-5-(4-methylsulfonylphenyl)-4-(2-chloro-4-methoxyphenyl) oxazole;
- 2-benzyl-5-(4-methylsulfonylphenyl)-4-(3-chloro-4-methoxyphenyl) oxazole;
- 30 2-benzyl-5-(4-methylsulfonylphenyl)-4-(3-chloro-2-methoxyphenyl) oxazole;
- 2-benzyl-5-(4-methylsulfonylphenyl)-4-(2-chloro-6-methoxyphenyl) oxazole;
- 35 2-benzyl-5-(4-methylsulfonylphenyl)-4-(4-chloro-2-methoxyphenyl) oxazole;

- 2-benzyl-5-(4-methylsulfonylphenyl)-4-(4-chloro-3-methoxyphenyl) oxazole;
- 2-benzyl-5-(4-methylsulfonylphenyl)-4-(3,5-dichloro-4-methoxyphenyl) oxazole;
- 5 2-benzyl-5-(4-methylsulfonylphenyl)-4-(2-fluoro-4-methylphenyl) oxazole;
- 2-benzyl-5-(4-methylsulfonylphenyl)-4-(3-fluoro-4-methylphenyl) oxazole;
- 2-benzyl-5-(4-methylsulfonylphenyl)-4-(3-fluoro-2-methylphenyl) oxazole;
- 10 2-benzyl-5-(4-methylsulfonylphenyl)-4-(2-fluoro-6-methylphenyl) oxazole;
- 2-benzyl-5-(4-methylsulfonylphenyl)-4-(4-fluoro-2-methylphenyl) oxazole;
- 15 2-benzyl-5-(4-methylsulfonylphenyl)-4-(4-fluoro-3-methylphenyl) oxazole;
- 2-benzyl-5-(4-methylsulfonylphenyl)-4-(2-fluoro-4-methoxyphenyl) oxazole;
- 2-benzyl-5-(4-methylsulfonylphenyl)-4-(3-fluoro-4-methoxyphenyl) oxazole;
- 20 2-benzyl-5-(4-methylsulfonylphenyl)-4-(3-fluoro-2-methoxyphenyl) oxazole;
- 2-benzyl-5-(4-methylsulfonylphenyl)-4-(2-fluoro-6-methoxyphenyl) oxazole;
- 25 2-benzyl-5-(4-methylsulfonylphenyl)-4-(4-fluoro-2-methoxyphenyl) oxazole;
- 2-benzyl-5-(4-methylsulfonylphenyl)-4-(2-thienyl) oxazole;
- 2-benzyl-5-(4-methylsulfonylphenyl)-4-(5-chloro-2-thienyl) oxazole;
- 30 2-benzyl-5-(4-methylsulfonylphenyl)-4-(cyclohexyl) oxazole;
- 2-benzyl-5-(4-methylsulfonylphenyl)-4-(1-cyclohexenyl) oxazole;
- 35 2-benzyl-5-(4-methylsulfonylphenyl)-4-(2-cyclohexenyl) oxazole;

- 2-benzyl-5-(4-methylsulfonylphenyl)-4-(3-cyclohexenyl)oxazole;
2-(ethyl)-5-(4-methylsulfonylphenyl)-4-phenyloxazole;
5 2-(trifluoromethyl)-5-(4-methylsulfonylphenyl)-4-phenyloxazole;
2-(difluoromethyl)-5-(4-methylsulfonylphenyl)-4-phenyloxazole;
2-(hydroxymethyl)-5-(4-methylsulfonylphenyl)-4-phenyloxazole;
10 [5-(4-methylsulfonylphenyl)-4-phenyl]-2-oxazolecarboxylic acid;
methyl [5-(4-methylsulfonylphenyl)-4-phenyl]-2-oxazolecarboxylate;
15 ethyl [5-(4-methylsulfonylphenyl)-4-phenyl]-2-oxazolecarboxylate;
2-(propyl)-5-(4-methylsulfonylphenyl)-4-phenyloxazole;
2-(benzyl)-5-(4-methylsulfonylphenyl)-4-phenyloxazole;
20 2-(phenylthiomethyl)-5-(4-methylsulfonylphenyl)-4-phenyloxazole;
2-(phenoxymethyl)-5-(4-methylsulfonylphenyl)-4-phenyloxazole;
25 2-((4-chlorophenoxy)methyl)-5-(4-methylsulfonylphenyl)-4-phenyloxazole;
2-((3-chlorophenoxy)methyl)-5-(4-methylsulfonylphenyl)-4-phenyloxazole;
2-((2-chlorophenoxy)methyl)-5-(4-methylsulfonylphenyl)-4-phenyloxazole;
30 2-((4-fluorophenoxy)methyl)-5-(4-methylsulfonylphenyl)-4-phenyloxazole;
2-((3-fluorophenoxy)methyl)-5-(4-methylsulfonylphenyl)-4-phenyloxazole;
35 2-((2-fluorophenoxy)methyl)-5-(4-methylsulfonylphenyl)-4-phenyloxazole;

- 2-((4-carboxyphenoxy)methyl)-5-(4-methylsulfonylphenyl)-4-phenyloxazole;
2-((3-carboxyphenoxy)methyl)-5-(4-methylsulfonylphenyl)-4-phenyloxazole;
5 2-((2-carboxyphenoxy)methyl)-5-(4-methylsulfonylphenyl)-4-phenyloxazole;
2-(2-phenethyl)-5-(4-methylsulfonylphenyl)-4-phenyloxazole;
2-(3-phenylpropyl)-5-(4-methylsulfonylphenyl)-4-phenyloxazole;
10 [5-(4-methylsulfonylphenyl)-4-phenyl]-2-oxazoleacetic acid;
ethyl [5-(4-methylsulfonylphenyl)-4-phenyl]-2-oxazoleacetate;
15 methyl [5-(4-methylsulfonylphenyl)-4-phenyl]-2-oxazoleacetate;
[5-(4-methylsulfonylphenyl)-4-phenyl]-2-oxazolepropanoic acid;
ethyl [5-(4-methylsulfonylphenyl)-4-phenyl]-2-oxazolepropanoate;
20 methyl [5-(4-methylsulfonylphenyl)-4-phenyl]-2-oxazolepropanoate;
[5-(4-methylsulfonylphenyl)-4-phenyl]-2-oxazolebutanoic acid;
25 ethyl [5-(4-methylsulfonylphenyl)-4-phenyl]-2-oxazolebutanoate;
methyl [5-(4-methylsulfonylphenyl)-4-phenyl]-2-oxazolebutanoate;
2-(2-quinolyloxymethyl)-5-(4-methylsulfonylphenyl)-4-phenyloxazole;
30 4-[2-(ethyl)-4-phenyl-5-oxazolyl]benzenesulfonamide;
4-[2-(trifluoromethyl)-4-phenyl-5-oxazolyl]benzenesulfonamide;
4-[2-(difluoromethyl)-4-phenyl-5-oxazolyl]benzenesulfonamide;
35 4-[2-(hydroxymethyl)-4-phenyl-5-oxazolyl]benzenesulfonamide;

- [5-(4-aminosulfonylphenyl)-4-phenyl]-2-oxazolecarboxylic acid;
methyl [5-(4-aminosulfonylphenyl)-4-phenyl]-2-oxazolecarboxylate;
5 ethyl [5-(4-aminosulfonylphenyl)-4-phenyl]-2-oxazolecarboxylate;
4-[2-(propyl)-4-phenyl-5-oxazolyl]benzenesulfonamide;
4-[2-(benzyl)-4-phenyl-5-oxazolyl]benzenesulfonamide;
10 4-[2-(phenylthiomethyl)-4-phenyl-5-oxazolyl]benzenesulfonamide;
4-[2-(phenoxyethyl)-4-phenyl-5-oxazolyl]benzenesulfonamide;
15 4-[2-((4-chlorophenoxy)methyl)-4-phenyl-5-oxazolyl]benzenesulfonamide;
4-[2-((3-chlorophenoxy)methyl)-4-phenyl-5-oxazolyl]benzenesulfonamide;
4-[2-((2-chlorophenoxy)methyl)-4-phenyl-5-oxazolyl]benzenesulfonamide;
20 4-[2-((4-fluorophenoxy)methyl)-4-phenyl-5-oxazolyl]benzenesulfonamide;
4-[2-((3-fluorophenoxy)methyl)-4-phenyl-5-oxazolyl]benzenesulfonamide;
25 4-[2-((2-fluorophenoxy)methyl)-4-phenyl-5-oxazolyl]benzenesulfonamide;
4-[2-((4-carboxyphenoxy)methyl)-4-phenyl-5-oxazolyl]benzenesulfonamide;
4-[2-((3-carboxyphenoxy)methyl)-4-phenyl-5-oxazolyl]benzenesulfonamide;
30 4-[2-((2-carboxyphenoxy)methyl)-4-phenyl-5-oxazolyl]benzenesulfonamide;
4-[2-(2-phenethyl)-4-phenyl-5-oxazolyl]benzenesulfonamide;
35 4-[2-(3-phenylpropyl)-4-phenyl-5-oxazolyl]benzenesulfonamide;

- [5-(4-aminosulfonylphenyl)-4-phenyl]-2-oxazoleacetic acid;
- methyl [5-(4-aminosulfonylphenyl)-4-phenyl]-2-oxazoleacetate;
- 5 ethyl [5-(4-aminosulfonylphenyl)-4-phenyl]-2-oxazoleacetate;
- [5-(4-aminosulfonylphenyl)-4-phenyl]-2-oxazolepropanoic acid;
- methyl [5-(4-aminosulfonylphenyl)-4-phenyl]-2-oxazolepropanoate;
- 10 ethyl [5-(4-aminosulfonylphenyl)-4-phenyl]-2-oxazolepropanoate;
- [5-(4-aminosulfonylphenyl)-4-phenyl]-2-oxazolebutanoic acid;
- 15 methyl [5-(4-aminosulfonylphenyl)-4-phenyl]-2-oxazolebutanoate;
- ethyl [5-(4-aminosulfonylphenyl)-4-phenyl]-2-oxazolebutanoate;
- 4-[2-(2-quinolyloxymethyl)-4-phenyl-5-oxazolyl]benzenesulfonamide;
- 20 5-(4-fluorophenyl)-2-methyl-4-[4-(methylsulfonyl)phenyl]oxazole;
- 3-[5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]]-2-oxazolepropanoic acid;
- 25 methyl 3-[5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]]-2-oxazolepropanoate;
- 4-(4-fluorophenyl)-2-(2-phenylethyl)-5-(4-(methylsulfonyl)phenyl)oxazole;
- 4-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]oxazole;
- 30 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyloxazole;
- 2-benzyl-4-(4-fluorophenyl)-5-(4-(methylsulfonyl)phenyl)oxazole;
- 35 4-(4-fluorophenyl)-5-[4-methylsulfonylphenyl]-2-(3-phenylpropyl)oxazole;

- 4-(4-fluorophenyl)-5-[4-methylsulfonylphenyl]-2-propyloxazole;
- 2-(*tert*-butyl)-4-(4-fluorophenyl)-5-[4-methylsulfonylphenyl]oxazole;
- 5 4-(4-fluorophenyl)-2-[(4-methoxyphenyl)methyl]-5-[4-methylsulfonylphenyl]oxazole
- 4-(4-fluorophenyl)-2-[(3-methoxyphenyl)methyl]-5-[4-methylsulfonylphenyl]oxazole;
- 2-(diphenylmethyl)-4-(4-fluorophenyl)-5-[4-methylsulfonylphenyl]oxazole;
- 10 2-[4-(4-fluorophenyl)-5-[4-methylsulfonylphenyl]]-2-oxazoleacetic acid;
- ethyl 2-[4-(4-fluorophenyl)-5-[4-methylsulfonylphenyl]]-2-oxazoleacetate;
- 15 3-[4-(4-fluorophenyl)-5-[4-methylsulfonylphenyl]]-2-oxazolepropanoic acid;
- methyl 3-[4-(4-fluorophenyl)-5-[4-methylsulfonylphenyl]]-2-oxazolepropanoate;
- 4-[4-(4-fluorophenyl)-5-[4-methylsulfonylphenyl]]-2-oxazolebutanoic acid;
- 20 methyl 4-[4-(4-fluorophenyl)-5-[4-methylsulfonylphenyl]]-2-oxazolebutanoate;
- 3-[4-(4-fluorophenyl)-5-[4-methylsulfonylphenyl]]-2-oxazolepropanamide;
- 25 4-(4-fluorophenyl)-2-(cyclohexylethyl)-5-[4-(methylsulfonyl)phenyl]oxazole;
- 4-(4-fluorophenyl)-2-(3-fluorophenoxymethyl)-5-[4-(methylsulfonyl)phenyl]oxazole;
- 4-(4-fluorophenyl)-2-(3-chlorophenoxymethyl)-5-[4-(methylsulfonyl)phenyl]oxazole;
- 30 4-(4-fluorophenyl)-2-(pyridyloxymethyl)-5-[4-(methylsulfonyl)phenyl]oxazole;
- 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenoxyethyl oxazole;
- 35 4-(4-fluorophenyl)-2-(2-hydroxyethyl)-5-[4-(methylsulfonyl)phenyl]oxazole;

- 4-(4-fluorophenyl)-2-(hydroxymethyl)-5-[4-(methylsulfonyl)phenyl]oxazole;
 4-(cyclohexyl)-2-phenyl-5-[4-(methylsulfonyl)phenyl]oxazole;
 5 4-(4-fluorophenyl)-2-benzyloxymethyl-5-[4-(methylsulfonyl)phenyl]oxazole;
 4-(4-fluorophenyl)-2-cyclohexyl-5-[4-(methylsulfonyl)phenyl]oxazole;
 5-(4-fluorophenyl)-2-phenyl-4-[4-(methylsulfonyl)phenyl]oxazole;
 10 (methylsulfonyl)phenyl]oxazole;
 [5-(3,4-dichlorophenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide;
 4-[4-(3-aminosulfonyl-5-fluoro-4-methoxyphenyl)-2-trifluoromethyl-5-oxazolyl]benzenesulfonamide;
 15 4-(3-fluoro-4-methoxyphenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethyloxazole;
 4-[4-(4-bromophenyl)-2-methyl-5-oxazolyl]benzenesulfonamide;
 20 5-fluoro-4-methoxy-3-[5-phenyl-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide;
 4-[4-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl-5-oxazolyl]benzenesulfonamide;
 ethyl 4-[[5-(4-aminosulfonylphenyl)-4-phenyl-2-oxazolyl]oxy]benzoate; and
 25 4-[5-(3-chloro-4-fluorophenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide.

- The term "hydrido" denotes a single hydrogen atom (H).
 30 This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical or two hydrido radicals may be attached to a carbon atom to form a methylene (-CH₂-) radical. Where the term "alkyl" is used, either alone or within other terms such as "haloalkyl",
 35 "alkoxyalkyl" and "hydroxyalkyl", embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More

preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, 5 isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl and the like. The term "alkenyl" embraces linear or branched radicals having at least one carbon-carbon double bond of two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms, 10 provided that the double bond does not directly bond to the oxazole ring. More preferred alkenyl radicals are "lower alkenyl" radicals having two to about six carbon atoms. Examples of such radicals include ethenyl, n-propenyl, butenyl, and the like. The term "alkynyl" embraces linear 15 or branched radicals having two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms, and containing a carbon-carbon triple bond. The more preferred "lower alkynyl" are radicals having two to ten carbons. Examples of such radicals include ethynyl, 1- or 2- 20 propynyl, 1-, 2- or 3-butyne and the like and isomers thereof. The term "halo" means halogens such as fluorine, chlorine, bromine or iodine. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically 25 embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of 30 different halo radicals. "Lower haloalkyl" embraces radicals having 1-6 carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, trichloromethyl, pentafluoroethyl, 35 heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. The term "hydroxyalkyl"

embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. More preferred hydroxyalkyl radicals are "lower hydroxyalkyl" radicals having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl. The term "hydroxyalkenyl" embraces linear or branched alkenyl radicals having three to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. The term "hydroxyalkynyl" embraces linear or branched alkynyl radicals having three to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about twelve carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and tert-butoxy. The term "alkoxyalkyl" embraces alkyl radicals having one or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. The "alkoxy" or "alkoxyalkyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkoxy or haloalkoxyalkyl radicals. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl and biphenyl. Preferred aryl radicals are those consisting of one, two, or three benzene rings. Aryl moieties may also be substituted at a substitutable position with one or more substituents selected independently from alkyl, alkoxyalkyl, alkylaminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, alkoxy, amino, halo, nitro, alkylamino, alkylcarbonylamino, alkylsulfonyl, arylsulfonyl, alkynyl, hydroxyalkynyl, aminoalkynyl, heteroarylalkynyl, heteroaralkyl, alkenyl, acyl, cyano, carboxy, aminocarbonyl, alkoxycarbonyl and alkylthio. The terms "heterocyclyl" or "heterocyclic"

embrace saturated, partially saturated and unsaturated heteroatom-containing ring-shaped radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. Examples of saturated heterocyclic radicals include

5 saturated 5 to 7-membered heteromonocyclic group containing 1 to 4 nitrogen atoms [e.g. pyrrolidinyl, imidazolidinyl, piperidinyl, piperazinyl, tropanyl, homotropanyl, etc.]; saturated 5 to 7-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g.

10 morpholinyl, etc.]; saturated 5 to 7-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., thiazolidinyl, etc.]. Examples of partially saturated heterocyclic radicals include dihydrothiophene, dihydropyran, oxazolinyl, dihydrofuran

15 and dihydrothiazole. Examples of unsaturated heterocyclic radicals, also termed "heteroaryl" radicals include unsaturated 5 to 7 membered heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidyl,

20 azepinyl, pyrazinyl, pyridazinyl, triazolyl [e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.] tetrazolyl [e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.], etc.; unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl,

25 indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g., tetrazolo[1,5-b]pyridazinyl, etc.], etc.; unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, furyl, etc.; unsaturated 5 to

30 7-membered heteromonocyclic group containing a sulfur atom, for example, thienyl, etc.; unsaturated 5 to 7-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl,

35 1,2,5-oxadiazolyl, etc.] etc.; unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzoxazolyl, benzoxadiazolyl,

etc.]; unsaturated 5 to 7-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl [e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.]
5 etc.; unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., benzothiazolyl, benzothiadiazolyl, etc.] and the like. The term also embraces radicals where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic
10 radicals include benzofuryl, benzothienyl, and the like. The heterocyclyl moieties may also be substituted at a substitutable position with one or more substituents selected independently from alkyl, alkoxyalkyl, alkylaminoalkyl, carboxyalkyl, alkoxycarbonylalkyl,
15 aminocarbonylalkyl, alkoxy, amino, halo, nitro, alkylamino, alkylcarbonylamino, alkylsulfonyl, alkynyl, alkenyl, arylsulfonyl, acyl, cyano, carboxy, aminocarbonyl, alkoxycarbonyl and alkylthio. The term "aralkyl" embraces aryl-substituted alkyl radicals. Preferable aralkyl
20 radicals are "lower aralkyl" radicals having aryl radicals attached to alkyl radicals having one to six carbon atoms. Examples of such radicals include benzyl, diphenylmethyl, triphenylmethyl, phenylethyl and diphenylethyl. The terms benzyl and phenylmethyl are interchangeable. The term
25 "heterocyclylalkyl" embraces saturated and partially unsaturated heterocyclyl-substituted alkyl radicals, such as pyrrolidinylmethyl, and heteroaryl-substituted alkyl radicals, such as pyridylmethyl, quinolylmethyl, thienylmethyl, furylethyl, and quinolylethyl. The term
30 "aryloxy" embrace oxy-containing aryl radicals attached through an oxygen atom to other radicals. More preferred aryloxy radicals are "lower aryloxy" radicals having a phenyl radical. An example of such radicals is phenoxy. The term "aryloxyalkyl" embraces alkyl radicals having one or
35 more aryloxy radicals attached to the alkyl radical, that is, to form monoaryloxyalkyl and diaryloxyalkyl radicals. The "aryloxy" or "aryloxyalkyl" radicals may be further

substituted on the aryl rings as defined above. The term "aralkyloxy" embrace oxy-containing aralkyl radicals attached through an oxygen atom to other radicals. The "aralkoxy" radicals may be further substituted on the aryl
5 ring portion of the radical as described above. The term "aralkyloxyalkyl" embraces alkyl radicals having one or more aralkyloxy radicals attached to the alkyl radical, that is, to form monoaralkyloxyalkyl and diaralkyloxyalkyl radicals. The "aralkyloxy" or "aralkyloxyalkyl" radicals
10 may be further substituted on the aryl ring portion of the radical. The term "heteroaryloxyalkyl" embraces alkyl radicals having one or more heteroaryloxy radicals attached to the alkyl radical, that is, to form monoheteroaryloxyalkyl and diheteroaryloxyalkyl radicals.
15 The "heteroaryloxy" radicals may be further substituted on the heteroaryl ring portion of the radical. The term "arylthio" embraces radicals containing an aryl radical, as described above, attached to a divalent sulfur atom, such as a phenylthio radical. The term "arylthioalkyl" embraces
20 alkyl radicals substituted with one or more arylthio radicals, as described above. The term "cycloalkyl" embraces radicals having three to ten carbon atoms. More preferred cycloalkyl radicals are "lower cycloalkyl" radicals having three to seven carbon atoms. Examples
25 include radicals such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. The term "cycloalkylalkyl" embraces alkyl radicals substituted with cycloalkyl radicals having three to ten carbon atoms, such as cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cyclohexylethyl, cyclohexylpropyl and
30 cycloheptylmethyl. The term "cycloalkenyl" embraces unsaturated radicals having three to ten carbon atoms, such as cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl and cycloheptenyl. The term "sulfonyl", whether used alone
35 or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals $\text{-SO}_2\text{-}$. "Alkylsulfonyl" embraces alkyl radicals attached to a sulfonyl radical,

where alkyl is defined as above. The "alkylsulfonyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkylsulfonyl radicals. The term "alkylsulfinyl" embraces alkyl radicals attached to a sulfinyl ($-S(O)-$) radical, where alkyl is defined as above. More preferred alkylsulfinyl radicals are "lower alkylsulfinyl" radicals having one to six carbon atoms. Examples of such lower alkylsulfinyl radicals include methylsulfinyl, ethylsulfinyl, butylsulfinyl and hexylsulfinyl. The term "alkylthio" embraces alkyl radicals attached to a divalent sulfur radical, where alkyl is defined as above. More preferred alkylthio radicals are "lower alkylthio" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylthio radicals are methylthio, ethylthio, propylthio, butylthio and hexylthio. The terms "sulfamyl", "aminosulfonyl" and "sulfonamidyl" denote a sulfonyl radical substituted with an amine radical, forming a sulfonamide ($-SO_2NH_2$). The terms "alkylcarbonyl", "arylcarbonyl" and "aralkylcarbonyl" include radicals having alkyl, hydroxylalkyl, aryl, arylalkyl and arylhydroxylalkyl radicals, as defined herein, attached to a carbonyl radical. Examples of such radicals include substituted or unsubstituted methylcarbonyl, ethylcarbonyl, propylcarbonyl, butylcarbonyl, pentylcarbonyl, hydroxymethylcarbonyl, hydroxyethylcarbonyl, phenylcarbonyl, benzylcarbonyl, and phenyl(hydroxymethyl)carbonyl. The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes $-CO_2H$. The term "carboxyalkyl" embrace radicals having a carboxy radical as defined above, attached to an alkyl radical, which may be substituted, such as with halo radicals, or unsubstituted. More preferred are "lower carboxyalkyl" which embrace lower alkyl radicals as defined above, and may be additionally substituted on the alkyl radical with halo. Examples of such lower carboxyalkyl radicals include carboxymethyl,

carboxyethyl, carboxybutyl, carboxypentyl, carboxyhexyl and carboxypropyl. The term "acyl" denotes a radical provided by the residue after removal of hydroxyl from an organic acid. Examples of such acyl radicals include alkanoyl and aroyl radicals. Examples of such alkanoyl radicals include formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, and radicals formed from succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, mandelic, pantothenic, β -hydroxybutyric, galactaric and galacturonic acids. The term "aroyl" embraces aryl radicals with a carbonyl radical as defined below. Examples of aroyl include benzoyl, naphthoyl, phenylacetyl, and the like, and the aryl in said aroyl may be additionally substituted, such as in *p*-hydroxybenzoyl, and salicylyl. The term "carboxyalkylthio" embraces carboxyalkyl radicals as defined above, connected to a divalent sulfur atom. The term "alkoxycarbonyl" means a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a "carbonyl" ($-C=O$) radical. Examples of such "alkoxycarbonyl" ester radicals include substituted or unsubstituted methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl and hexyloxycarbonyl. The term "alkoxycarbonylalkyl" embraces alkyl radicals having one or more alkoxycarbonyl radicals attached to the alkyl radical. The term "phosphonylalkyl" describes alkyl radicals substituted with phosphonic acid residues or esters thereof. The term "aminoalkyl" embraces alkyl radicals substituted with amino radicals. More preferred are "lower aminoalkyl" radicals. Examples of such radicals include aminomethyl, aminoethyl, and the like. The term "aminocarbonyl" embraces radicals having an amino radical radicals attached to a carbonyl radical forming $-C(O)NH_2$. The term "aminocarbonylalkyl" embraces alkyl radicals having one or more aminocarbonyl radicals attached to the alkyl radical. The term "alkylaminocarbonylalkyl" embraces alkyl radicals having

aminocarbonyl radicals substituted with one or two alkyl radicals. Examples of such include N-alkylaminocarbonylalkyl and N,N-dialkylaminocarbonylalkyl radicals such as N-methylaminocarbonylmethyl and N,N-dimethylaminocarbonylmethyl. The term "alkylamino" denotes amino groups which have been substituted with one or two alkyl radicals. More preferred alkylamino radicals are "lower alkylamino" having alkyl radicals of one to six carbon atoms attached to the nitrogen atom of an amine. Suitable "lower alkylamino" may be mono or dialkylamino such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino or the like. "Amino acid residue" means any of the naturally occurring alpha-, beta- and gamma-amino carboxylic acids, including their D and L optical isomers and racemic mixtures thereof, synthetic amino acids, and derivatives of these natural and synthetic amino acids. The amino acid residue is bonded either through an amino or an acid functional group of the amino acid. The naturally occurring amino acids which can be incorporated in the present invention include, but are not limited to, alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, ornithine, phenylalanine, proline, serine, threonine, cyclohexylalanine, tryptophan, tyrosine, valine, β -alanine, and γ -aminobutyric acid. Derivatives of amino acids which can be incorporated in the present invention include, but are not limited to amino acids having protected and modified carboxylic acids, including acid esters and amides, protected amines, and substituted phenyl rings, including but not limited to alkyl, alkoxy and halo substituted tyrosine and phenylalanine.

The present invention comprises a pharmaceutical composition for the treatment of inflammation and inflammation-associated disorders, such as arthritis, comprising a therapeutically-effective amount of a compound

of Formula I in association with at least one pharmaceutically-acceptable carrier, adjuvant or diluent.

The present invention also comprises a therapeutic method of treating inflammation or inflammation-associated disorders in a subject, the method comprising treating the
5 subject having such inflammation or disorder a therapeutically-effective amount of a compound of Formula I.

The method of the present invention also includes prophylactic treatment. A preferred method
10 of the invention is the administration of water soluble compounds of Formulas III via injection.

Also included in the family of compounds of Formula I are the pharmaceutically-acceptable salts thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly
15 used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts of compounds of Formula I may be prepared from an inorganic
20 acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and
25 sulfonic classes of organic acids, example of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicylic, p-hydroxybenzoic,
30 phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethylsulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, stearic, cyclohexylaminosulfonic, algenic, β -hydroxybutyric, salicylic, galactaric and galacturonic
35 acid. Suitable pharmaceutically-acceptable base addition salts of compounds of Formula I include metallic salts made from aluminum, calcium, lithium, magnesium, potassium,

diastereoisomeric salts by treatment with an optically active acid or base. Examples of appropriate acids are tartaric, diacetyltartaric, dibenzoyltartaric, ditoluoyltartaric and camphorsulfonic acid and then

5 separation of the mixture of diastereoisomers by crystallization followed by liberation of the optically active bases from these salts. A different process for separation of optical isomers involves the use of a chiral chromatography column optimally chosen to maximize the

10 separation of the enantiomers. Still another available method involves synthesis of covalent diastereoisomeric molecules by reacting an amine functionality of precursors to compounds of Formula I with an optically pure acid in an activated form or an optically pure isocyanate.

15 Alternatively, diastereomeric derivatives can be prepared by reacting a carboxyl functionality of precursors to compounds of Formula I with an optically pure amine base. The synthesized diastereoisomers can be separated by conventional means such as chromatography, distillation,

20 crystallization or sublimation, and then hydrolyzed to deliver the enantiomerically pure compound. The optically sodium and zinc or organic salts made from N,N'-dibenzylethylenediamine, choline, chloroprocaine, diethanolamine, ethylenediamine, meglumine (N-

25 methylglucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compound of Formula I by reacting, for example, the appropriate acid or base with the compound of Formula I.

Also included in the family of compounds of Formula I

30 are the stereoisomers thereof. Compounds of the present invention can possess one or more asymmetric carbon atoms and are thus capable of existing in the form of optical isomers as well as in the form of racemic or nonracemic mixtures thereof. Accordingly, some of the compounds of

35 this invention may be present in racemic mixtures which are also included in this invention. The optical isomers can

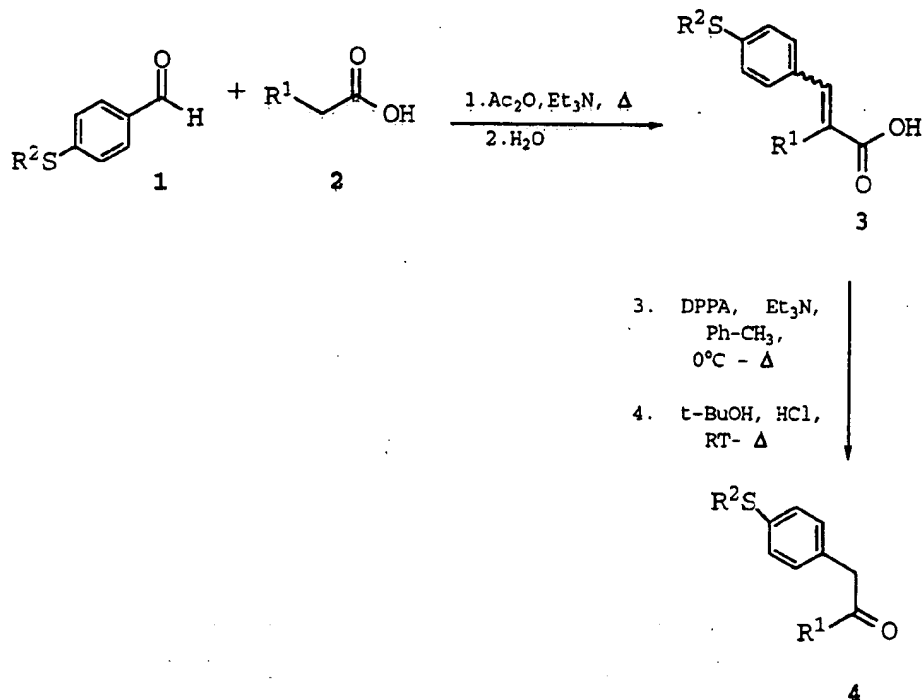
be obtained by resolution of the racemic mixtures according to conventional processes, for example by formation of active compounds of Formula I-III can likewise be obtained by utilizing optically active starting materials. These isomers may be in the form of a free acid, a free base, an ester or a salt.

Additional methods for resolving optical isomers, known to those skilled in the art may be used, for example, those discussed by J. Jaques et al in Enantiomers, Racemates, and Resolutions, John Wiley and Sons, New York (1981).

GENERAL SYNTHETIC PROCEDURES

The compounds of the invention can be synthesized according to the following procedures of Schemes I-XI, wherein the R-R⁸ substituents are as defined for Formula I-III, above, except where further noted.

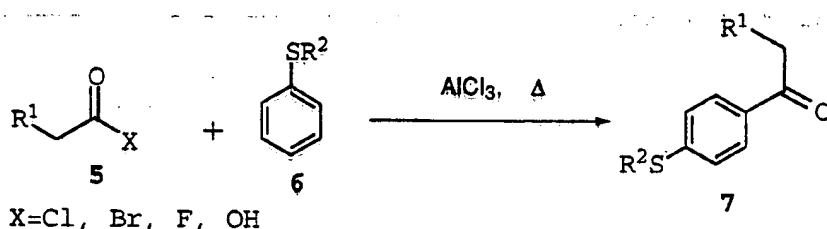
Scheme I



Synthetic Scheme I shows the four step procedure which can be used to prepare the substituted ketone

- compounds **4** from the substituted benzaldehyde **1** and acid **2**, where R^2 is alkyl. In step one, benzaldehyde **1** and substituted acetic acid **2** are first heated in acetic anhydride and triethylamine via a Perkin condensation.
- 5 In step two, hydrolysis produces the corresponding 2,3-disubstituted acrylic acids **3**. In step three, the acrylic acids **3** are reacted with diphenylphosphorylazide (DPPA) and triethylamine in toluene at 0°C and then warmed to room temperature to form acylazides. In step
- 10 four, the crude acylazides are heated to form an isocyanate via a Curtius rearrangement. The isocyanate is trapped as the N-*t*-butyloxycarbonyl enamine derivative via the addition of *tert*-butanol. Acidic hydrolysis, such as by using concentrated HCl, provides
- 15 the substituted ketone **4** intermediates.

Scheme II

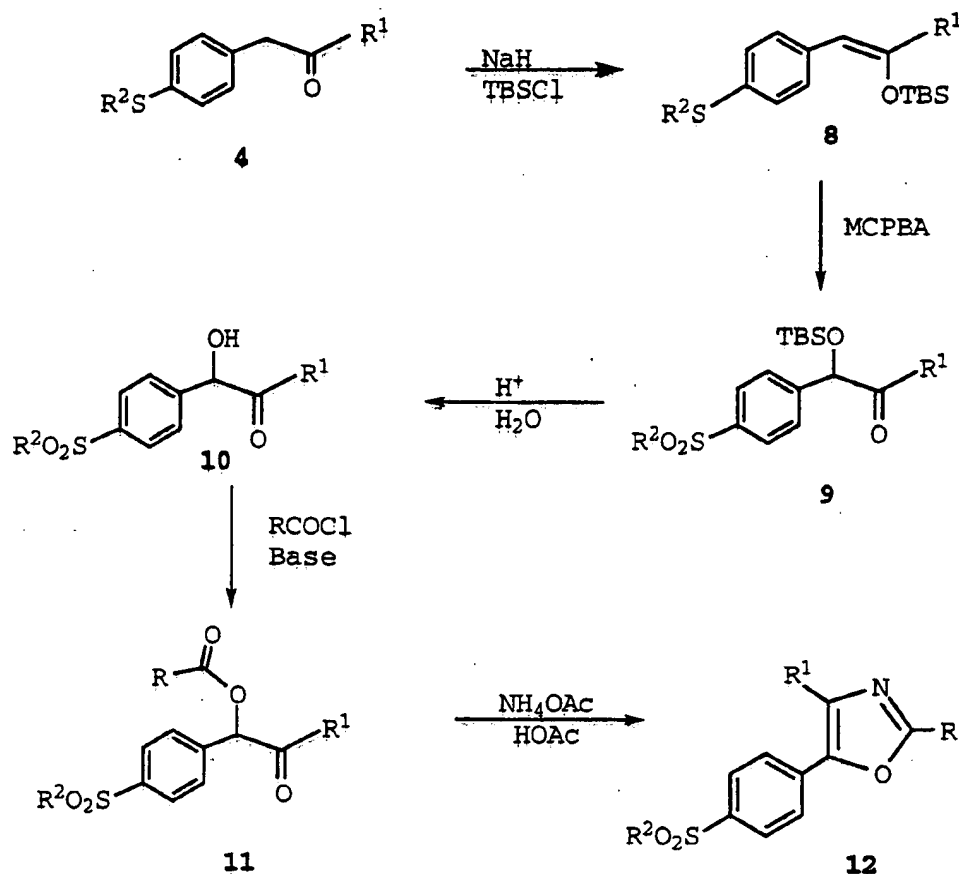


20

- Synthetic Scheme II shows an alternative approach which can be used to prepare substituted ketone intermediates **7**, isomers of **4** where R^2 is alkyl, via the use of Friedel-Crafts acylation. An acylating agent **5**, such as an acid chloride, is treated with aluminum chloride in an inert solvent, such as methylene chloride, chloroform, nitrobenzene, dichlorobenzene or chlorobenzene, and reacted with alkylthiobenzene **6** to form ketone **7**.

- 30 Other synthetic approaches are possible to form the desired ketones. These alternatives include reacting appropriate Grignard or lithium reagents with substituted acetic acids or corresponding esters.

Scheme III



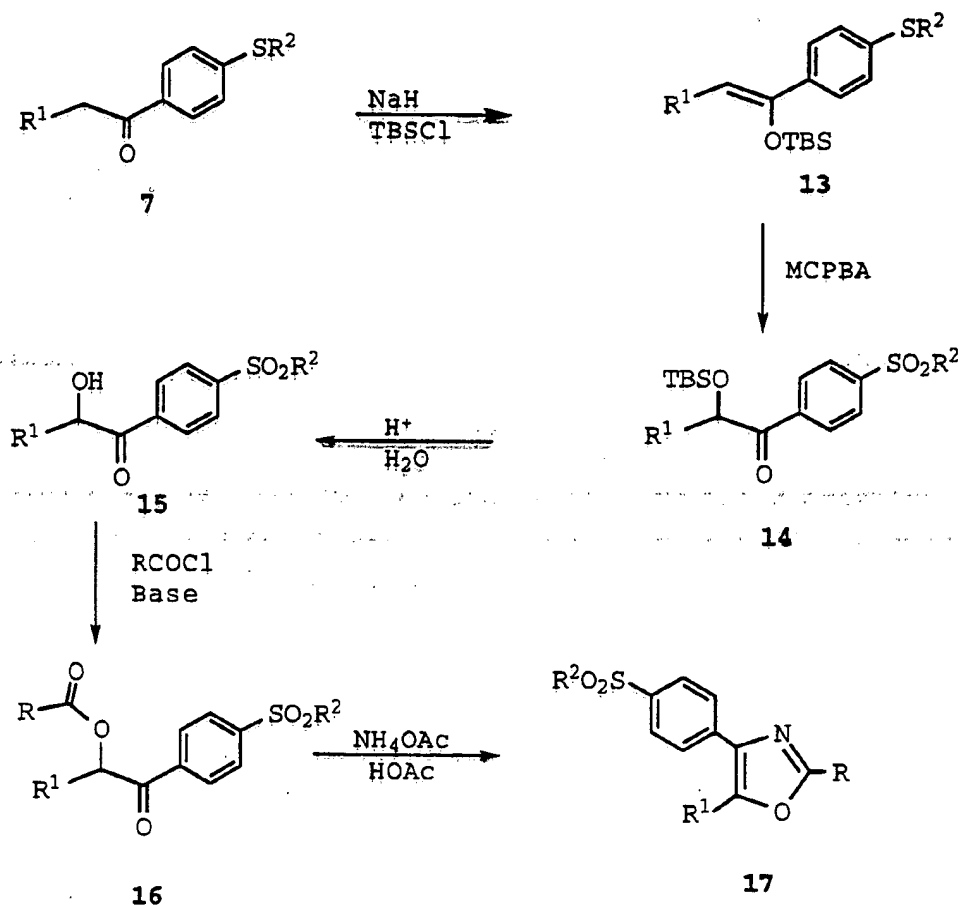
5

Scheme III shows the five step synthesis, as described in U.S. Patent No. 3,647,858, which can be used to prepare the 5-(4-alkylsulfonylphenyl)oxazoles 12 of Formula I from ketone 4 (prepared in Scheme I).

- 10 Preparation of the silyl enol ether 8 (where TBSCl is *tert*-butyl-dimethylsilyl chloride) is followed by oxidation, such as with *m*-chloroperoxybenzoic acid (MCPBA), to give the appropriate silylated benzoin 9.
- 15 Desilylation of this silylated benzoin 9 is achieved using aqueous acid, such as trifluoroacetic acid, to give the desired benzoin 10. Reaction of the benzoin 10 with the appropriate acid chloride in the presence of base, such as pyridine, gives the benzoin esters 11

which may be converted to the antiinflammatory oxazoles **12** of the present invention upon treatment with ammonium acetate in acetic acid at reflux.

5

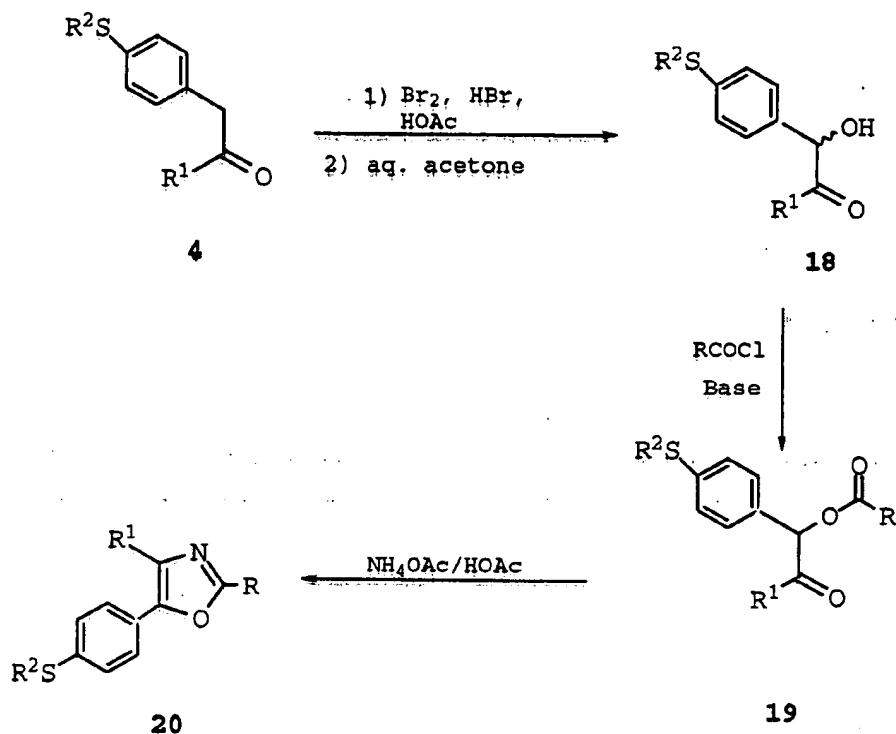
Scheme IV

Scheme IV shows the five step synthesis, similar to that described above in Scheme III, which can be used to prepare the 4-(4-alkylsulfonylphenyl) oxazoles **17** of Formula I from ketone **7** (prepared in Scheme II). Preparation of the silyl enol ether **13** is followed by oxidation, such as with *m*-chloroperbenzoic acid, to give the appropriate silylated benzoin **14**. Desilylation of this silylated benzoin **14** is achieved using aqueous acid, such as trifluoroacetic acid to give the desired benzoin **15**. Reaction of the benzoin **15** with the appropriate acid

chloride in the presence of base, such as pyridine, gives the benzoin esters 16 which may be converted to the antiinflammatory oxazoles 17 of the present invention upon treatment with ammonium acetate in acetic acid at reflux.

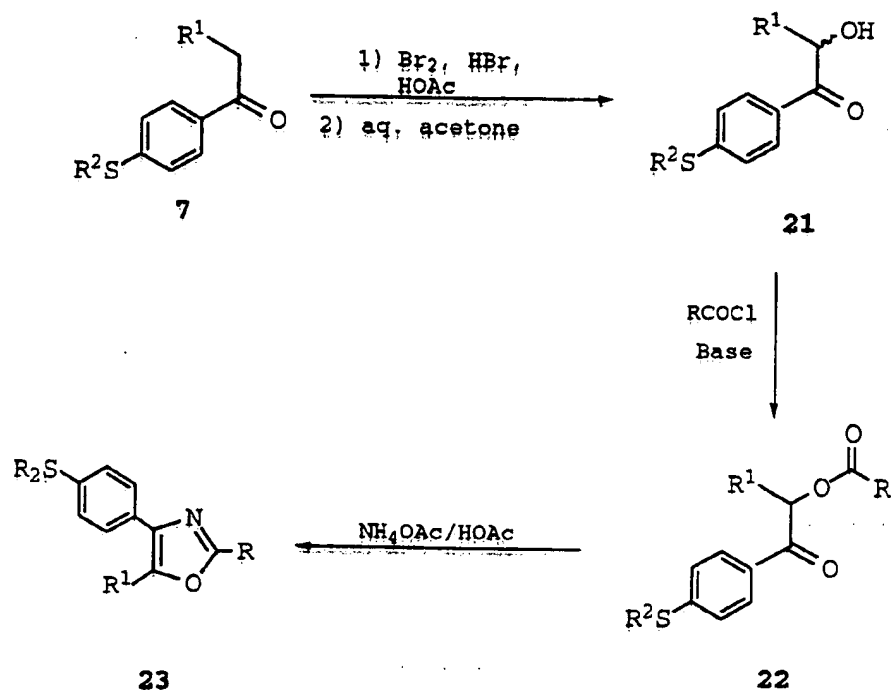
5

Scheme V



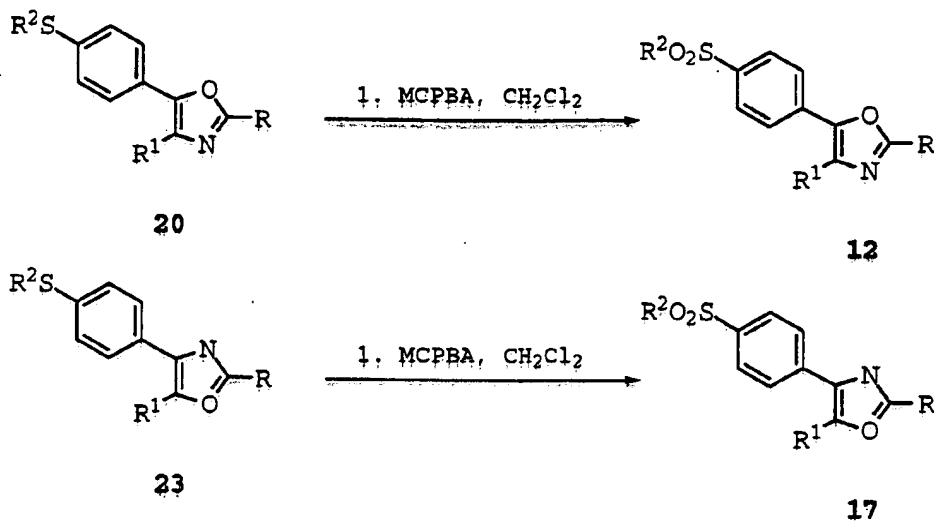
10 Scheme V shows the four step synthesis which can be
 used to prepare oxazoles 20 from ketones 4 (prepared in
 Synthetic Scheme I). In step one, ketones 4 are readily
 brominated via the addition of bromine in acetic acid to
 form the 2-bromoethanone intermediates. In step two,
 15 reaction of the bromoethanone with aqueous acetone yields
 the benzoin 18. In step three, reaction of the benzoin 18
 with the appropriate acid chloride in the presence of base,
 such as pyridine, gives the benzoin esters 19. In step
 four, benzoin esters 19 are converted to the oxazoles 20
 20 upon treatment with ammonium acetate in acetic acid at
 reflux.

Scheme VI



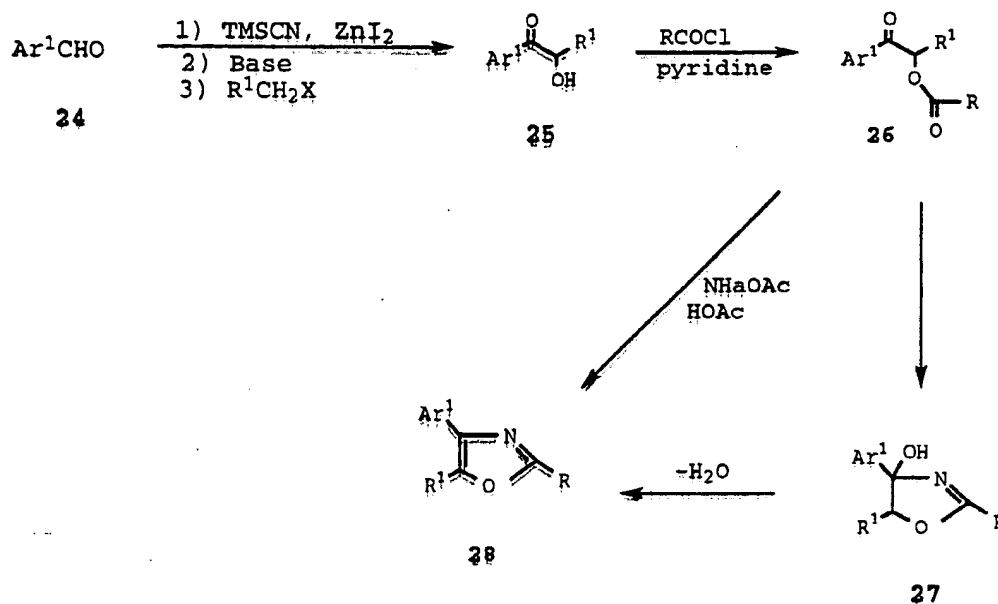
- 5 Similarly, Scheme VI shows the four step synthesis which can be used to prepare oxazoles **23** from ketones **7** (prepared in Synthetic Scheme II). In step one, ketones **7** are readily brominated via the addition of bromine in acetic acid to form the 2-bromoethanone intermediates. In
- 10 step two, reaction of the bromoethanone with aqueous acetone yields the benzoin **21**. In step three, reaction of the benzoin **21** with the appropriate acid chloride in the presence of base, such as pyridine, gives the benzoin esters **22**. In step four, benzoin esters **22** are converted
- 15 to the oxazoles **23** upon treatment with ammonium acetate in acetic acid at reflux.

Scheme VII



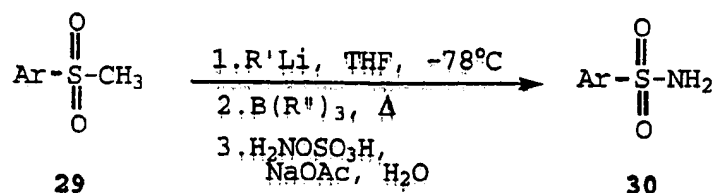
An alternative synthesis of the
5 alkylsulfonylphenyloxazoles 12 and 17 is accomplished as
shown in Synthetic Scheme VII from oxazoles 20 and 23
(prepared in Schemes V and VI). Oxazoles 20 and 23, where
R² is an alkyl radical, are oxidized, such as with MCPBA (2
equivalents) in methylene chloride to form the
10 antiinflammatory alkylsulfonyl oxazoles 12 and 17. Other
suitable oxidizing agents include Oxone®, hydrogen
peroxide, periodate, peracetic acid and the like.

Scheme VIII



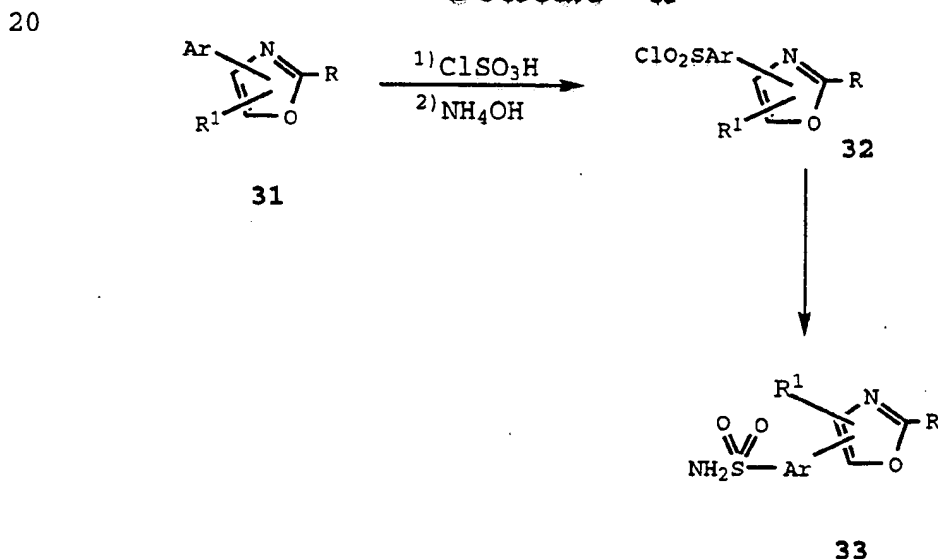
- 5 In a method similar to that shown in Scheme IV, Scheme VIII shows a method for preparing oxazoles 28 where Ar¹ represents an aromatic or heteroaryl radical without a sulfur substituent. A solution of aldehyde 24 and zinc iodide in an organic solvent such as dichloromethane (100
- 10 mL) is treated with trimethylsilylcyanide to give the trimethylsilyl cyanohydrin. The trimethylsilyl cyanohydrin is added to a solution of Ar¹-magnesium bromide in diethyl ether while maintaining the temperature between 25-35 °C to give the benzoin 25. The benzoin 25, pyridine, and acid chloride are reacted at room temperature to yield the
- 15 benzoin ester 26. Addition of ammonium acetate to the benzoin ester 26 yields the oxazole 28. Alternatively, the hydroxy-oxazoline 27 is isolated. Dehydration of the hydroxy-oxazoline 27 yields the oxazoles 28. By reversing
- 20 the positions of R¹ and Ar¹ in the keto-enol 25, oxazoles can be prepared with R¹ is at position 4.

Scheme IX



- 5 Synthetic Scheme VIII shows the three step procedure used to prepare sulfonamide antiinflammatory agents 30 from their corresponding methyl sulfones 29. In step one, a THF solution of the methyl sulfones 29 at about -78°C is treated with an alkyl lithium reagent, e.g., methyllithium, n-butyllithium, etc. In step two, the anions generated in
- 10 step one are treated with an organoborane, e.g., triethylborane, tributylborane, etc., at about -78°C then allowed to warm to ambient temperature prior to stirring at reflux. In step three, an aqueous solution of sodium
- 15 acetate and hydroxyamine-O-sulfonic acid is added to provide the corresponding sulfonamide antiinflammatory agents 30 of this invention.

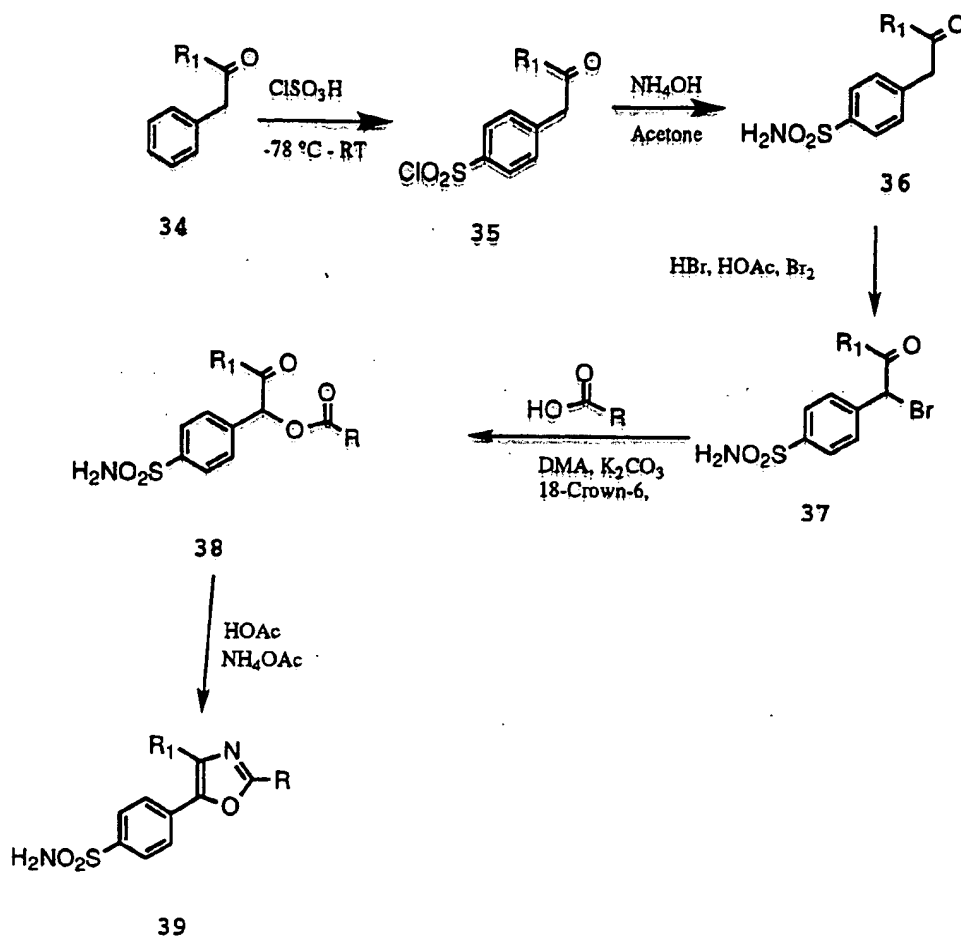
Scheme X



Scheme X shows another method of preparing oxazolybenzenesulfonamides 33 of the present invention. The oxazole 31 is stirred with chlorosulfonic acid at

about 5 °C to give the sulfonyl chlorides 32. The sulfonyl chloride 32 is reacted at about 5 °C with ammonium hydroxide to give the sulfonamides 33 of the current invention. In addition, disulfonamides can be formed by substitution on R¹ where R¹ is aryl or heteroaryl.

Scheme XI



10

Synthetic Scheme XI shows the five step procedure which can be used to prepare the substituted oxazolebenzenesulfonamide compounds 39, from the substituted ketone 34. The benzenesulfonamide 36 is formed, such as by adding the ketone 34 to chlorosulfonic acid at about -78 °C, then warming to room temperature to form the sulfonyl chloride 35. The sulfonyl chloride 35 is

15

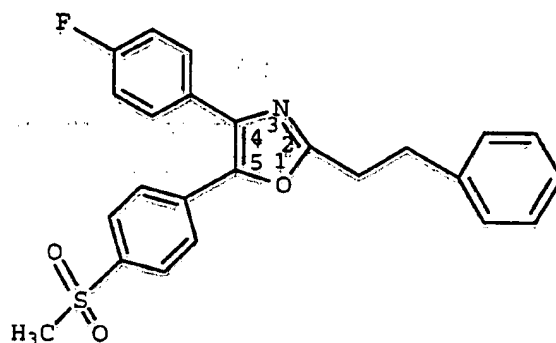
reacted with aqueous ammonium hydroxide in a solvent, such as acetone, at about 5 °C, and then at room temperature to form the sulfonamide 36. In step 3, the sulfonamide 36 is selectively brominated, such as with a solution of 30% HBr in acetic acid, acetic acid and bromine to form the bromoketone 37. In Step 4, the bromoketone 37 is added to an acid and potassium carbonate in dimethylacetamide to give the desired crude α -acyloxy ketone 38. In step 5, acetic acid and ammonium acetate are added to the acyloxy ketone 38, and heated, such as at about 100 °C to give the oxazole 39.

The following examples contain detailed descriptions of the methods of preparation of compounds of Formula I-III. These detailed descriptions fall within the scope, and serve to exemplify, the above described General Synthetic Procedures which form part of the invention. These detailed descriptions are presented for illustrative purposes only and are not intended as a restriction on the scope of the invention. All parts are by weight and temperatures are in Degrees centigrade unless otherwise indicated.

The following abbreviations are used:

EtOAc - ethyl acetate
NaOAc - sodium acetate
NaH - sodium hydride
25 NH₄OAc - ammonium acetate
HCl - hydrochloric acid
DMSO - dimethylsulfoxide
DMSO-d₆ - deuterated dimethylsulfoxide
CHCl₃ - chloroform
30 CD₃OD - deuterated methanol
MgSO₄ - magnesium sulfate
NaHCO₃ - sodium bicarbonate
Na₂SO₄ - sodium sulfate
DMF - dimethylformamide
35 CH₃CN - acetonitrile
CuI - copper iodide
NaOH - sodium hydroxide

- Pd/C - palladium on carbon
HBr - hydrobromic acid
K₂CO₃ - potassium carbonate
MeOH - methanol
5 EtOH - ethanol
LiOH - lithium hydroxide
CH₂Cl₂ - methylene chloride/dichloromethane
DBU - 1,8-diazabicyclo[5.4.0]undec-7-ene
h - hour
10 min - minutes
THF - tetrahydrofuran
HRMS - high resolution mass spectrum

EXAMPLE 1

4-(4-Fluorophenyl)-2-(2-phenylethyl)-5-(4-(methylsulfonyl)phenyl)oxazole

Step 1: Preparation of 1-(4-fluorophenyl)-2-hydroxy-2-(methylsulfonyl)phenyl)ethanone

- A suspension of 2.03 g sodium hydride in 125 mL tetrahydrofuran (THF) was stirred at 0°C under a nitrogen atmosphere as a solution containing 20.0 g of 1-(4-fluorophenyl)-2-[4-(methylthio)phenyl]ethanone, as prepared in U.S. Patent No. 3,647,858, in 100 mL of THF was added dropwise over 30 minutes. The reaction was allowed to warm to 25°C for 18 hours. A solution containing 12.7 g (84.5 mmol) of *tert*-butyl-

dimethylsilyl chloride (DBSCL) in 20 mL THF was added over 5 minutes and the resulting solution stirred at 25°C for 18 hours. The reaction was quenched by pouring into aqueous sodium bicarbonate. The mixture was
5 extracted with ethyl acetate and the combined organic extracts dried over sodium sulfate. Concentration in vacuo provides a yellow oil, which solidified on standing to give 27.9 g of the silyl enol ether. NMR spectra was consistent with the assigned structure. The
10 silyl enol ether was used without further purification.

A solution containing 27.9 g of the silyl enol ether in 500 mL methylene chloride (CH_2Cl_2) was cooled to 0°C under a nitrogen atmosphere while being stirred mechanically. 77.1g of *m*-chloroperoxybenzoic acid
15 (technical grade, 50-60%) was added and the reaction was stirred at 0°C for 2 hours and allowed to warm to 25°C over 1 hour. The reaction mixture was washed with an aqueous solution of sodium metabisulfite, followed by aqueous sodium bicarbonate. The organic solution was
20 dried over sodium sulfate and concentrated in vacuo to give 24.5 g of 1-(4-fluorophenyl)-2-tert-butyl dimethylsilyloxy-2-[4-(methylsulfonyl)phenyl]ethanone. NMR spectra were consistent with the assigned structure. This material
25 was used without further purification.

The benzoin silyl ether was dissolved in 100 mL of 90% aqueous trifluoroacetic acid and stirred at 25°C for 18 hours. The reaction was quenched by slowly pouring into saturated aqueous sodium bicarbonate solution. The
30 product was extracted with ethyl acetate and the combined organic extracts were dried over sodium sulfate. Concentration in vacuo provided an oily solid, which was recrystallized from 50% ethyl acetate/isooctane to give 15.5 g of a crystalline white
35 solid (mp 122-123°C) whose structure was assigned as 1-(4-fluorophenyl)-2-hydroxy-2-

(methylsulfonyl)phenyl)ethanone on the basis of its spectral properties.

The isomeric benzoin, 2-(4-fluorophenyl)-2-hydroxy-1-(4-(methylsulfonyl)phenyl)ethanone, was prepared analogously from 2-(4-fluorophenyl)-1-[4-(methylthio)phenyl] ethanone,

Step 2: Preparation of 4-(4-fluorophenyl)-2-(2-phenylethyl)-5-(4-(methylsulfonyl)phenyl)oxazole.

10 A solution containing 5.00 g of 1-(4-fluorophenyl)-2-hydroxy-2-(4-(methylsulfonyl)phenyl)ethanone in 100 mL methylene chloride (CH_2Cl_2) was stirred at 25°C as 6.60 mL of pyridine was added, followed by 3.61 mL of hydrocinnamoyl chloride.

15 The reaction was stirred at 25°C for 48 hours, after which the organic solution was washed with 1N HCl, dried over sodium sulfate and concentrated in vacuo to give an oily solid. This material was recrystallized from 50% ethyl acetate/isooctane to give 4.40 g of a

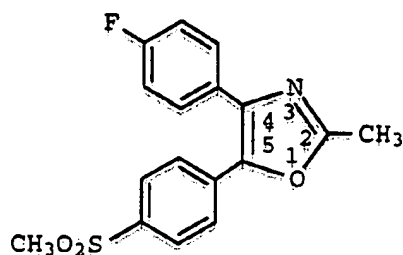
20 beige crystalline solid (mp 152-153.5°C). NMR spectra were consistent with the assigned structure of 1-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]-2-(2-phenyl)propionyloxy ethanone. This material was dissolved in 100 mL of glacial acetic acid and 7.70 g of

25 ammonium acetate was added. The reaction was heated to reflux with stirring for 1.5 hours, after which it was cooled to room temperature and poured into 100 mL of water. The product was extracted with ethyl acetate and the combined organic extracts washed with aqueous sodium

30 bicarbonate, dried over sodium sulfate and concentrated in vacuo to give an oily solid which was recrystallized from 50% ethyl acetate/isooctane to give 3.55 g of 4-(4-fluorophenyl)-2-(2-phenylethyl)-5-(4-(methylsulfonyl)phenyl)oxazole as a white crystalline solid (mp 117-

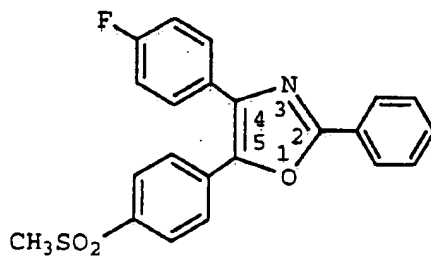
35 118°C). NMR spectra was consistent with the assigned structure.

70

EXAMPLE 2

5 4-(4-Fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]oxazole

4-(4-Fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]oxazole was prepared in an
 10 analogous manner to that shown in Example 1. Melting point: 158-159 °C.

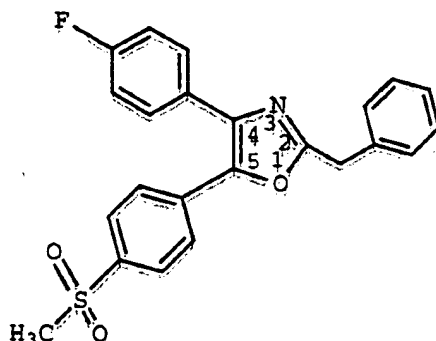
EXAMPLE 3

15

4-(4-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyloxazole

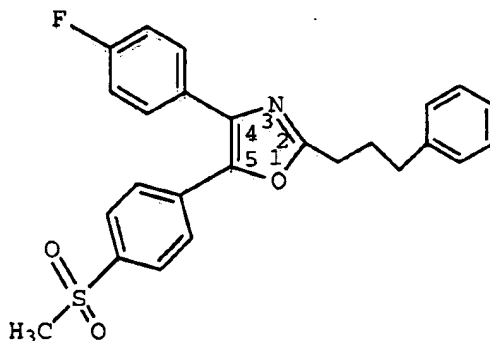
20 4-(4-Fluorophenyl)-5-[4-(methylsulfonyl) phenyl]-2-phenyloxazole was prepared in a manner analogous to Example 1. Melting point: 204-205 °C.

71

EXAMPLE 4

5 **2-Benzyl-4-(4-fluorophenyl)-5-(4-**
 (methylsulfonyl)phenyl)oxazole

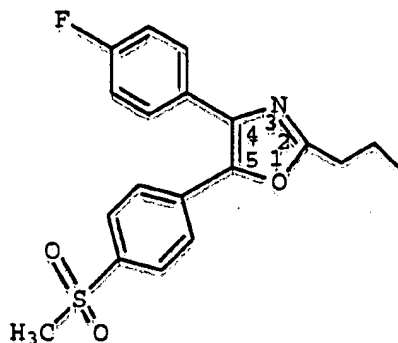
 2-Benzyl-4-(4-fluorophenyl)-5-(4-
 (methylsulfonyl)phenyl)oxazole was prepared in a manner
 10 analogous to Example 1. The m/z 408 (M+H)⁺ was
 consistent with the assigned structure.

EXAMPLE 5

15

4-(4-Fluorophenyl)-5-[4-methylsulfonylphenyl]-2-
 (3-phenylpropyl)oxazole

20 4-(4-Fluorophenyl)-5-[4-methylsulfonyl phenyl]-2-
 (3-phenylpropyl)oxazole was prepared in a manner
 analogous to Example 1. The m/z 436 (M+H)⁺ was
 consistent with the assigned structure.

EXAMPLE 6

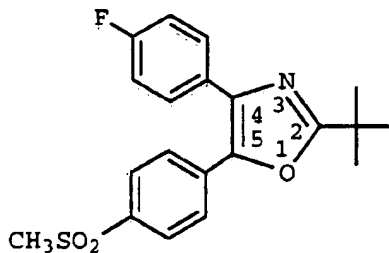
5

4-(4-Fluorophenyl)-5-[4-methylsulfonylphenyl]-2-propyloxazole

4-(4-Fluorophenyl)-5-[4-methylsulfonyl phenyl]-2-propyloxazole was prepared in a manner analogous to Example 1. The m/z 360 (M+H)⁺ was consistent with the assigned structure.

EXAMPLE 7

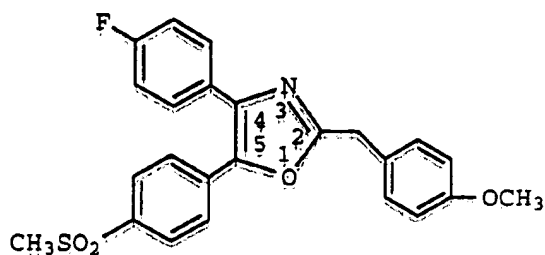
15



2-(*tert*-Butyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazole

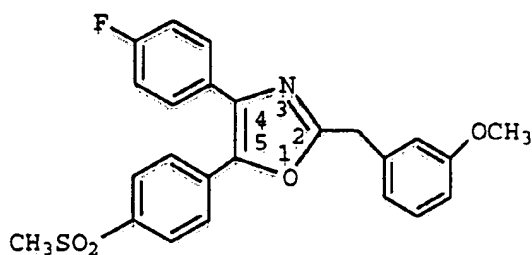
20

2-(*Tert*-butyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazole was prepared in a manner analogous to Example 1. Melting point: 130-131°C.

EXAMPLE 8

5 4-(4-Fluorophenyl)-2-(4-methoxyphenyl)methyl-5-
 [4-methylsulfonylphenyl]oxazole

 4-(4-Fluorophenyl)-2-(4-methoxyphenyl)methyl-5-[4-
methylsulfonylphenyl]oxazole was prepared in a manner
10 analogous to Example 1. Melting point: 123-124°C.

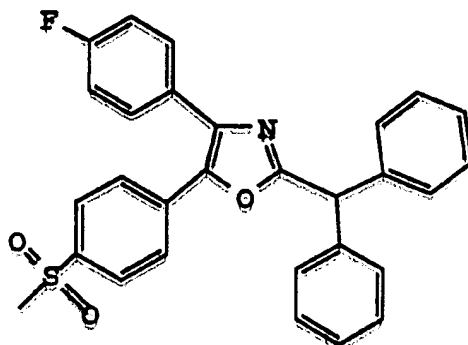
EXAMPLE 9

15

 4-(4-Fluorophenyl)-2-(3-methoxyphenyl)methyl-5-
 [4-methylsulfonylphenyl]oxazole

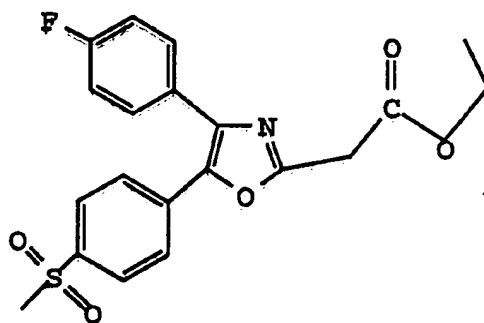
 4-(4-Fluorophenyl)-2-(3-methoxyphenyl)methyl-5-[4-
20 methylsulfonylphenyl]oxazole was prepared in a manner
analogous to Example 1. The m/z 437 (M+H)⁺ was
consistent with the assigned structure.

74

EXAMPLE 10

5 2-Diphenylmethyl-4-(4-fluorophenyl)-5-[4-methylsulfonylphenyl]oxazole

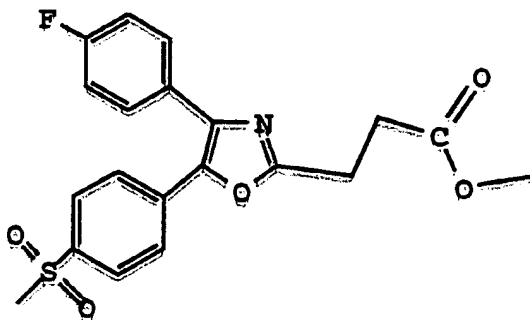
2-Diphenylmethyl-4-(4-fluorophenyl)-5-[4-methylsulfonylphenyl]oxazole was prepared in a manner
 10 analogous to Example 1. Melting point: 155-156°C.

EXAMPLE 11

15

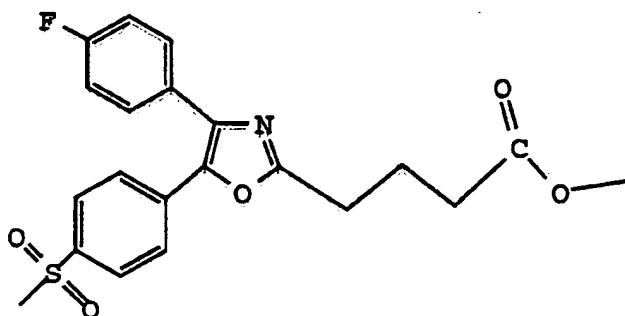
Ethyl 2-[4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)]-2-oxazoleacetate

Ethyl 2-[4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)]-2-oxazoleacetate was prepared in a
 20 manner analogous to Example 1. Melting point: 123-124°C.

EXAMPLE 12

5 Methyl 3-[4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)]-2-oxazolepropanate

 Methyl 3-[4-(4-fluorophenyl)-5-[4-methylsulfonylphenyl]oxazol-2-yl]propanate was prepared
10 in a manner analogous to Example 1. The m/z 404 (M+H)⁺ was consistent with the assigned structure.

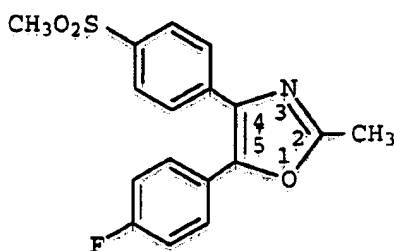
EXAMPLE 13

15

 Methyl 4-[4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)]-2-oxazolebutanate

20 Methyl 4-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]]-2-oxazolebutanate was prepared
in a manner analogous to Example 1. Melting point: 89-91°C.

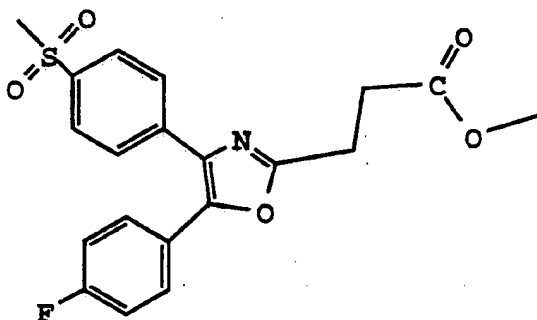
76

EXAMPLE 14

5 **5-(4-Fluorophenyl)-2-methyl-4-[4-(methylsulfonyl)phenyl]oxazole**

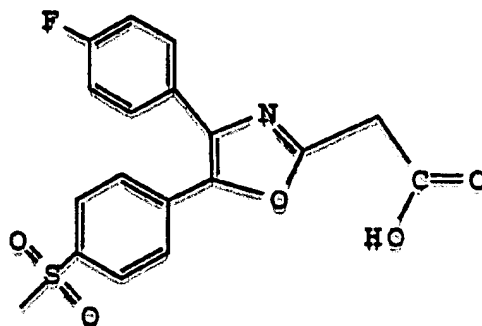
5-(4-Fluorophenyl)-2-methyl-4-[4-(methylsulfonyl)phenyl]oxazole was prepared in a manner analogous to
 10 Example 1 but with 2-(4-fluorophenyl)-1-[4-(methylthio)phenyl]ethanone as the starting material.
 The m/z 332 (M+H)⁺ was consistent with the assigned structure.

15 **EXAMPLE 15**



20 **Methyl 3-[5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]]-2-oxazolepropanoate**

Methyl 3-[5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]]-2-oxazolepropanoate was
 prepared in a manner analogous to Example 14. The m/z
 25 404 (M+H)⁺ was consistent with the assigned structure.

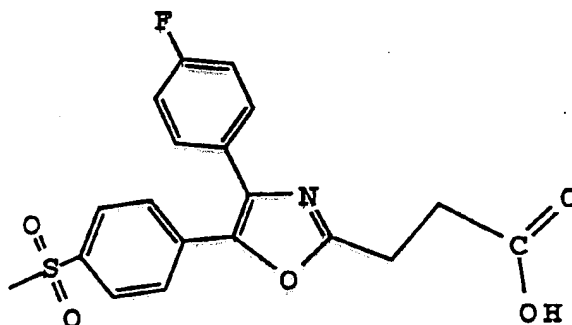
EXAMPLE 16

5

2-[4-(4-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]]-2-oxazoleacetic acid

2-[4-(4-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]acetic acid was prepared from Example 11 via alkaline hydrolysis using 1 N sodium hydroxide in methanol and appropriate reaction conditions. Melting point: 118-120°C.

15

EXAMPLE 17

3-[4-(4-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]]-2-oxazolepropanoic acid

20

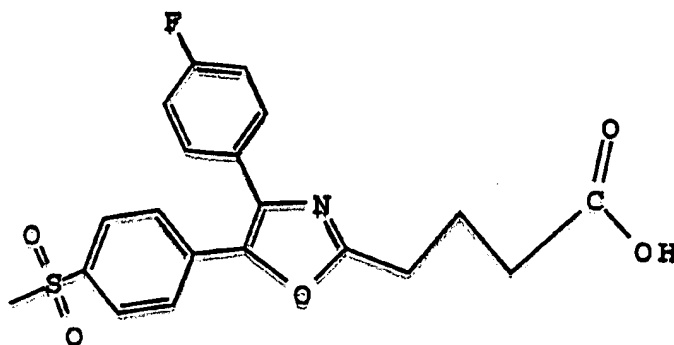
3-[4-(4-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]]-2-oxazolepropanoic acid was prepared from Example 12 in a manner analogous to Example 17. Melting

78

point: 197-198°C. The m/z 390 (M+H)⁺ was consistent with the assigned structure.

EXAMPLE 18

5

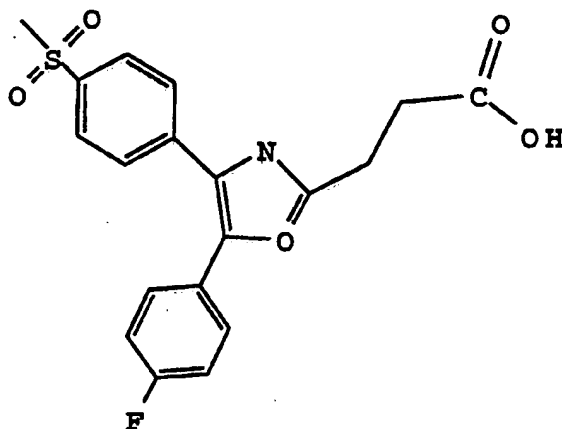


4-[4-(4-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]]-2-oxazolebutanoic acid

10

4-[4-(4-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]]-2-oxazolebutanoic acid was prepared from Example 13 in a manner analogous to Example 17. Melting point: 140-141°C. The m/z 404 (M+H)⁺ was consistent with the assigned structure.

15

EXAMPLE 19

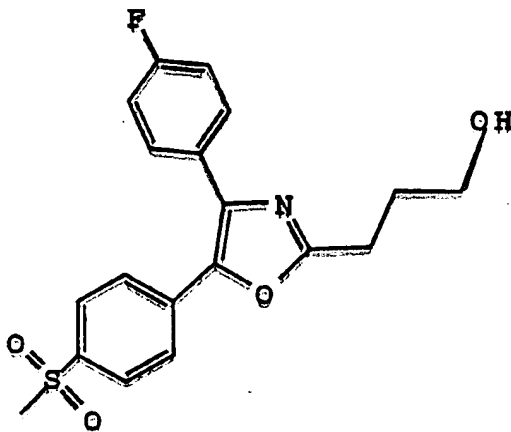
20

3-[5-(4-Fluorophenyl)-4-[4-(methylsulfonyl)phenyl]]-2-oxazolepropanoic acid

3-[5-(4-Fluorophenyl)-4-[4-(methylsulfonyl)phenyl]]-2-oxazolpropanoic acid was prepared from Example 15 in a manner analogous to Example 17. The m/z 390 (M+H)⁺ was consistent with the assigned structure.

5

EXAMPLE 20

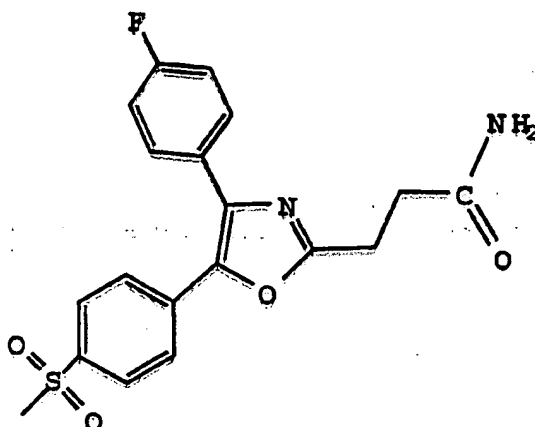


10 4-(4-Fluorophenyl)-2-(3-hydroxypropyl)-5-[4-(methylsulfonyl)phenyl]oxazole

A solution containing 100 mg (0.239 mmol) of 3-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]propanoic acid, methyl ester in 10 mL of tetrahydrofuran was cooled to 0°C with stirring under a nitrogen atmosphere as 0.53 mL of diisobutylaluminum hydride (1M in toluene, 0.523 mmol) was added dropwise over 5 minutes. The reaction was allowed to warm to 25°C and poured into 100 mL of a saturated solution of sodium potassium tartarate. Ethyl acetate (100 mL) was added and the mixture was stirred until the layers separated (approx. 1 hour). The organic layer was separated and dried over sodium sulfate. Concentration in vacuo gave an oily solid, which was recrystallized from 50 % ethyl acetate-isooctane to give 75 mg of a white crystalline solid (mp 123-124°C) which was characterized on the basis of its spectral

characteristics: $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 2.10 (m, 2H),
2.56 (bs, 1H), 3.01 (t, 2H, $J=7.0$ Hz), 3.07 (s, 3H),
3.80 (t, 2H, $J=5.9$ Hz), 7.09 (t, 2H, $J=8.5$ Hz), 7.57
(dd, 2H, $J=8.5$ and 5.5 Hz), 7.73 (d, 2H, $J=8.5$ Hz) and
5 7.89 (d, 2H, $J=8.5$ Hz), $^{19}\text{F-NMR}$ (CDCl_3 , 280 MHz) δ
-111.97. LRMS m/z 376 ($M + H$), HRMS calc. for
 $\text{C}_{19}\text{H}_{18}\text{NO}_4\text{FS}$: 376.1019, Observed: 376.1026. Analysis
calc. for $\text{C}_{19}\text{H}_{18}\text{NO}_4\text{FS-C}$: 60.79, H: 4.83, N: 3.73.
Observed-C: 60.53, H: 4.85, N: 3.66.

10

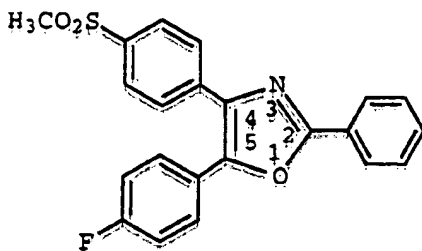
EXAMPLE 21

15

3-[4-(4-Fluorophenyl)-5-[4-(methanesulfonyl)phenyl]]-2-oxazopropanamide

3-[4-(4-fluorophenyl)-5-[4-(methanesulfonyl)phenyl]]-2-oxazopropanamide was prepared by treating
20 methyl 3-[4-(4-fluorophenyl)-5-(4-(methanesulfonyl)phenyl)-2-oxazopropanoic acid,
(Example 12) with excess ammonia in methanol for 5 days.
Melting point: 193-195°C.

EXAMPLE 22



5 5-(4-Fluorophenyl)-2-phenyl-4-[4-
 (methylsulfonyl)phenyl]oxazole

Step 1: Preparation of 5-(fluorophenyl)-4-[4-
(methylthio)phenyl]-2-phenyloxazole

- 10 A solution containing 560 mg (2.03 mmol) of 2-(4-fluorophenyl)-2-hydroxy-1-[4-(methylthio)phenyl] ethanone in 50 mL of methylene chloride was stirred at 25°C as 0.82 mL (10.15 mmol) of pyridine was added, followed by 0.28 mL (2.44 mmol) of benzoyl chloride.
- 15 The reaction was stirred at 25°C for 2 days, after which it was washed with 1N HCl, dried over sodium sulfate and concentrated in vacuo to give a crude oil which was characterized as the benzoin ester on the basis of its spectral characteristics: ¹H-NMR (CDCl₃, 300 MHz) δ 2.53
- 20 (s, 3H), 7.08 (s, 1H), 7.12 (t, 2H, J=8.7 Hz), 7.27 (d, 2H, J=8.7 Hz), 7.49 (t, 2H, J=7.7 Hz), 7.60 (m, 3H), 7.94 (d, 2H, J=8.7 Hz) and 8.14 (d, 2H, J=8.7 Hz). This material was dissolved in 50 mL of glacial acetic acid and 1.56 g (20.3 mmol) of ammonium acetate was added.
- 25 The reaction was heated at reflux for 2 hours, cooled to 25°C and poured into 100 mL of water. The aqueous solution was extracted with ethyl acetate and the combined organic extracts were washed with water and sodium bicarbonate solution, dried over sodium sulfate
- 30 and concentrated in vacuo. The crude solid was purified by flash chromatography using a silica gel column and 50% ethyl acetate/hexane as the eluent to give a white

solid which was recrystallized from 50% ethyl acetate/isooctane to give 450 mg (61%) of a white crystalline solid (mp 118-119°C) whose structure was assigned as 5-(4-fluorophenyl)-4-[4-(methylthio)phenyl]-2-phenyl oxazole on the basis of its spectral characteristics: $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 2.52 (s, 3H), 7.10 (t, 2H, $J=8.8$ Hz), 7.28 (d, 2H, $J=8.5$ Hz), 7.47 (m, 3H), 7.62 (m, 4H) and 8.13 (m, 2H). $^{19}\text{F-NMR}$ (CDCl_3 , 280 MHz) δ -111.96. LRMS m/z 361 (M)+. HRMS Calc'd. for $\text{C}_{22}\text{H}_{16}\text{NOFS}$: 361.0937. Observed: 361.0970. Analysis Calc'd. for $\text{C}_{22}\text{H}_{16}\text{NOFS}$: C, 71.51; H, 6.55; N, 3.79. Observed: C, 72.85; H, 4.52; N, 3.84.

Step 2: Preparation of 5-(4-fluorophenyl)-4-[4-(methylsulfinyl)phenyl]-2-phenyloxazole.

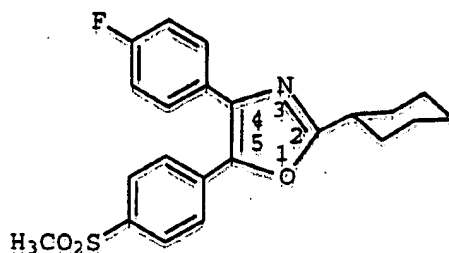
A solution containing 64 mg (0.173 mmol) of 5-(4-fluorophenyl)-4-[4-(methylthio)phenyl]-2-phenyloxazole in 10 mL of methylene chloride was stirred at -78°C as 60 mg (0.173 mmol based on 50% purity) of *m*-chloroperoxybenzoic acid was added all at once. The reaction was stirred at -78°C for 1 hour. Thin-layer chromatography (TLC) (silica, 50% hexane-ethyl acetate) indicated that the reaction mixture consisted of mostly sulfoxide, with a minor amount of sulfide and sulfone. The reaction was poured into a solution of aqueous sodium metabisulfite. The aqueous solution was extracted using ethyl acetate and the organic layer was washed with saturated sodium metabisulfite, saturated sodium bicarbonate and brine. The resulting clear solution was dried over sodium sulfate and concentrated *in vacuo* to give a white solid which was purified by flash chromatography on a silica gel column using 50% ethyl acetate/hexane as the eluent. Recrystallization from 50% ethyl acetate/isooctane gave 48 mg (74%) of a white crystalline solid (mp 164-165°C) whose structure was assigned as 5-(4-fluorophenyl)-4-[4-(methylsulfinyl)phenyl]-2-phenyl oxazole on the basis of

its spectral characteristics: $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 2.80 (s, 3H), 7.16 (t, 2H, $J=8.5$ Hz), 7.54 (m, 3H), 7.66-7.75 (m, 4H), 7.93 (d, 2H, $J=8.5$ Hz) and 8.19 (m, 2H). LRMS m/z 377 (M) $^+$, HRMS Calc'd. for $\text{C}_{22}\text{H}_{16}\text{NO}_2\text{FS}$: 377.0886. Observed: 377.0868. Analysis Calc'd. for $\text{C}_{22}\text{H}_{16}\text{NO}_2\text{FS}$: C, 70.01; H, 4.27; N, 3.71. Observed: C, 68.18; H, 4.19; N, 3.58.

10 Step 3: Preparation of 5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2-phenyloxazole.

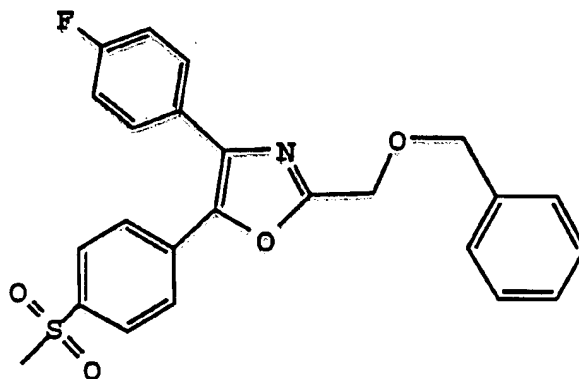
A solution containing 64 mg (0.173 mmol) of 5-(4-fluorophenyl)-4-[4-(methylthio)phenyl]-2-phenyloxazole in 10 mL of methylene chloride was stirred at -78°C as 120 mg (0.346 mmol based on 50% purity) of *m*-chloroperoxybenzoic acid was added all at once. The reaction was stirred at -78°C for 1 hour and TLC (silica, 50% hexane-ethyl acetate) indicated that the reaction mixture consisted of mostly sulfone. The reaction was poured into a solution of aqueous sodium metabisulfite. The aqueous solution was extracted using ethyl acetate and the organic layer was washed with saturated sodium metabisulfite, saturated sodium bicarbonate and brine. The resulting clear solution was dried over sodium sulfate and concentrated in vacuo to give a white solid which was purified by flash chromatography on a silica gel column using 50% ethyl acetate/hexane as the eluent. Recrystallization from 50% dichloromethane/isooctane gave 62 mg (91%) of a white crystalline solid (mp $175-176^\circ\text{C}$) whose structure was assigned as 5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2-phenyl oxazole on the basis of its spectral characteristics: $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 3.13 (s, 3H), 7.19 (t, 2H, $J=8.6$ Hz), 7.55 (m, 3H), 7.69 (m, 2H), 8.00 (m, 2H), 8.17 (m, 2H). LRMS m/z 393 (M) $^+$. HRMS Calc'd. for $\text{C}_{22}\text{H}_{16}\text{NO}_3\text{FS}$: 393.0835. Observed: 393.0865.

84

EXAMPLE 23

5 **2-Cyclohexyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazole**

2-Cyclohexyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazole was prepared in a manner
 10 analogous to Example 1. Melting point: 127-128°C.

EXAMPLE 24

15

2-Benzyloxymethyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazole

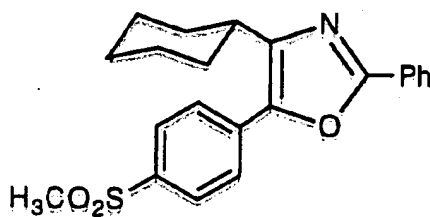
Step 1: Preparation of the benzoin ester

20 A solution containing 2.07 g (6.71 mmol) of 1-(4-fluorophenyl)-2-hydroxy-2-[4-(methylsulfonylphenyl)ethanone in 100 mL of methylene chloride was stirred at 25°C as 2.71 mL (33.55 mmol) of pyridine was added, followed by the addition of 1.27 mL

(8.05 mmol) of benzyloxyacetyl chloride. The reaction was stirred at 25°C for 48 hours, after which the resulting yellow solution was washed with 1N HCl, dried over sodium sulfate and concentrated in vacuo. The oily yellow solid was purified via flash chromatography on a silica gel column using 20 % ethyl acetate/hexane as the eluent. This provided 2.22 g (73 %) of a white foam, which was characterized as the benzoin ester on the basis of its NMR spectra: ¹H-NMR (CDCl₃, 300 MHz) δ 3.03 (s, 3H), 4.23 (d, 1H, J=17.0 Hz), 4.33 (d, 1H, J=17.0 Hz), 4.67 (s, 2H), 6.95 (s, 1H), 7.13 (t, 2H, J=8.5 Hz), 7.35 (m, 5H), 7.66 (d, 2H, J=8.1 Hz) and 7.98 (m, 4H). ¹⁹F-NMR (CDCl₃, 280 MHz) δ -102.5.

15 Step 2: Preparation of 2-benzyloxymethyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazole.

A solution containing 2.22 g (4.86 mmol) of the benzoin ester and 3.74 g (48.6 mmol) of ammonium acetate in 100 mL of acetic acid was heated to 80°C for 2 hours. The reaction was cooled to 25°C and poured into water. The product was extracted into ethyl acetate and the combined organic extracts washed with an aqueous solution of sodium bicarbonate. The solution was dried over sodium sulfate and concentrated in vacuo to give a yellow oil. This crude material was purified by flash chromatography on a silica gel column using 25 % ethyl acetate/hexane as the eluent to give 1.92 g (90%) of a clear oil, which was characterized as 2-benzyloxymethyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazole on the basis of its spectral properties: ¹H-NMR (CDCl₃, 300 MHz) δ 3.07 (s, 3H), 4.70 (s, 2H), 4.72 (s, 2H), 7.11 (t, 2H, J=8.8 Hz), 7.22-7.40 (m, 5H), 7.58 (m, 2H), 7.76 (d, 2H, J=8.8 Hz) and 7.91 (d, 2H, J=8.8 Hz). ¹⁹F-NMR (CDCl₃, 280 MHz) δ -111.88.

EXAMPLE 25

5 **4-(Cyclohexyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyloxazole**

Step 1: Preparation of 1-(cyclohexyl)-2-hydroxy-2-[4-(methylthiophenyl)ethanone

10 A 250 mL round bottomed flask was equipped with a mechanical stirrer and reflux condenser and charged with 30 mL of absolute ethanol, 3,4-dimethyl-5-(2-hydroxyethyl)thiazolium iodide (2.00 g, 7.0 mmol), 4-methylthiobenzaldehyde (10.66 g, 70.0 mmol), and freshly
 15 distilled cyclohexanecarboxaldehyde (7.68 g, 70.1 mmol). The solution was stirred vigorously, treated with triethylamine (4.27 g, 42.2 mmol) and heated to reflux for 24 hours. The solution was treated with additional portions of 3,4-dimethyl-5-(2-hydroxyethyl)thiazolium
 20 iodide (2.05 g, 7.01 mmol), triethylamine (4.84 g, 48.0 mmol), and cyclohexanecarboxaldehyde (7.01 g, 62.5 mmol), and heated to reflux for an additional 42 hours. The solution was concentrated in vacuo, the residue dissolved in chloroform, washed with 3 N HCl, saturated
 25 aqueous sodium bicarbonate, brine, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to afford 18.75 g, (>100%) of a yellow oil that solidified upon standing. The crude solid was purified by
 30 trituration with ether providing the desired compound in pure form 15.80 g, (86%, mp 110-111.5°C) which was characterized as 1-(cyclohexyl)-2-hydroxy-2-[4-(methylthiophenyl)ethanone on the basis of its NMR spectra. ¹H-NMR (CDCl₃, 300 MHz) δ 1.00-1.47 (m, 6H),

1.60-1.95 (m, 4H), 2.45 (m, 1H), 2.52 (s, 3H), 4.38 (d, J=3.9 Hz, 1H), 7.55 (d, J=3.9 Hz, 1H), 7.25 (m, 4H).
HRMS Calc'd. for $C_{15}H_{20}NO_2S$: 264.1184. Observed: 264.1207.

5

Step 2: Preparation of benzoin ester

A solution containing 162 mg (0.62 mmol) of 1-(cyclohexyl)-2-hydroxy-2-[4-(methylthiophenyl) ethanone in 10 mL of methylene chloride was stirred at 25°C as
10 251 μ L (31 mmol) of pyridine was added, followed by the addition of 86 μ L (1.24 mmol) of benzoyl chloride. The reaction was stirred at 25°C for 48 hours, after which the resulting yellow solution was washed with 1N HCl, dried over sodium sulfate and concentrated in vacuo.
15 The crude solid was purified via flash chromatography on a silica gel column using 10 % ethyl acetate/hexane as the eluent. This provided 131 mg (57 %) of a white foam, which was characterized as the benzoin ester on the basis of its NMR spectra: 1H -NMR ($CDCl_3$, 300 MHz) δ
20 1.03-1.48 (m, 6H), 1.56-1.88 (m, 3H), 2.03-2.14 (m, 1H), 2.48 (s, 3H), 2.53 (m, 1H), 6.28 (s, 1H), 7.20-7.70 (m, 5H), 8.05-8.17 (m, 4H).

Step 3: Preparation of 4-cyclohexyl-5-[4-(methylthio)phenyl]-2-phenyloxazole

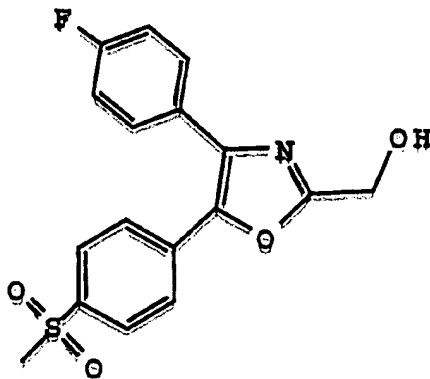
25 A solution containing 131 mg (0.355 mmol) of the benzoin ester and 273 mg (35 mmol) of ammonium acetate in 10 mL of acetic acid was heated to 80°C for 2 hours. The reaction was cooled to 25°C and poured into water.
30 The product was extracted into ethyl acetate and the combined organic extracts washed with an aqueous solution of sodium bicarbonate. The solution was dried over sodium sulfate and concentrated in vacuo to give the crude oxazole. This crude material was purified
35 crystallization from a mixture of dichloromethane and isooctane to give 89 mg, (72%, mp 151-151.5°C) of material, which was characterized as 4-(cyclohexyl)-5-

[4-(methythio)phenyl]-2-phenyloxazole on the basis of its spectral properties: $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 1.30-1.45 (m, 3H), 1.70-1.94 (m, 7H), 2.54 (s, 3H), 2.80-2.90 (m, 1H), 7.34 (d, $J=8.5\text{Hz}$, 2H), 7.42 (m, 3H), 7.55 (d, $J=8.5\text{Hz}$, 2H), 8.08 (d, $J=7.7\text{Hz}$, 2H). HRMS Calc'd. for $\text{C}_{22}\text{H}_{23}\text{NOS}$ (M+H): 350.1579. Observed: 350.1597. The material from this experiment was used directly in the next step without further purification.

10 Step 4: Preparation of 4-(cyclohexyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyloxazole

A solution of 38 mg (0.11 mmol) of 2-phenyl-4-(cyclohexyl)-5-[4-(methythio)phenyl]oxazole in 4 mL of methylene chloride was stirred at -78°C as 75 mg (0.22 mmol based on 50% purity) of *m*-chloroperoxybenzoic acid was added all at once. The reaction was stirred at -78°C for 1 hour. Thin-layer chromatography (TLC) (silica, 50% hexane/ethyl acetate) indicated the reaction mixture consisted of mostly sulfone. The reaction was poured into a solution of aqueous sodium metabisulfite. The aqueous solution was extracted using ethyl acetate and the organic layer was washed with saturated sodium metabisulfite, saturated sodium bicarbonate and brine. The resulting clear solution was dried over sodium sulfate and concentrated *in vacuo* to give a white solid which was purified by crystallization from 50% dichloromethane/isooctane gave 26 mg (62%) of pure product, whose structure was assigned as 4-(cyclohexyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyloxazole on the basis of its spectral characteristics: mp 231°C . $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 1.34-1.43 (m, 3H), 1.72-1.95 (m, 7H), 2.84 (m, 1H), 3.10 (s, 3H), 7.47 (m, 3H), 7.82 (d, $J=8\text{Hz}$, 2H), 8.03 (d, $J=8\text{Hz}$, 2H), 8.10 (m, 2H). LRMS m/z 382 (M)+. HRMS Calc'd. for $\text{C}_{22}\text{H}_{23}\text{NO}_3\text{S}$: 382.1477. Observed: 382.1436. Analysis Calc'd. for $\text{C}_{22}\text{H}_{23}\text{NO}_3\text{S}$: C, 69.27; H, 6.08; N, 3.67. Observed: C, 68.99; H, 6.07; N, 3.63.

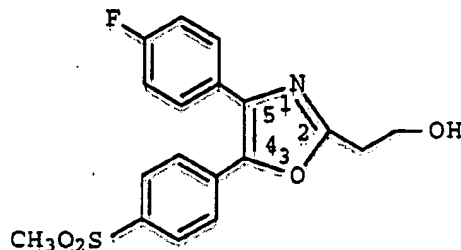
EXAMPLE 26



5

4-(4-Fluorophenyl)-2-(hydroxymethyl)-5-[4-(methylsulfonyl)phenyl]oxazole

To a solution containing 5.0 g (11.4 mmol) of 2-benzyloxymethyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazole (prepared in Example 24) in 20 mL of 50 % THF-methanol, was added 100 mg of 10% Pd on charcoal in a Fisher-Porter bottle. The reaction vessel was evacuated and then charged with hydrogen at 50 psi for 24 hours. The Pd on carbon was removed by filtration through diatomaceous earth and the filtrate concentrated in vacuo to give 3.8 g (97 %) of a white crystalline solid (mp 156-157°C) (recrystallized from 50% ethyl acetate/isooctane) whose structure was assigned as 4-(4-fluorophenyl)-2-hydroxymethyl-5-[4-(methylsulfonyl)phenyl]oxazole on the basis of its spectral characteristics: ¹H-NMR (CDCl₃, 300 MHz) δ 3.07 (s, 3H), 3.21 (bs, 1H), 4.81 (s, 2H), 7.10 (t, 2H, J=8.5 Hz), 7.56 (m, 2H), 7.72 (d, 2H, J=8.8 Hz) and 7.90 (d, 2H, J=8.8 Hz). ¹⁹F-NMR (CDCl₃, 280 MHz) δ -111.5. LRMS m/z 348 (M + H)⁺. HRMS Calc'd. for C₁₇H₁₄NO₄FS: 348.0706. Observed: 348.0681. Analysis Calc'd. for C₁₇H₁₄NO₄FS: C, 58.78; H, 4.06; N, 4.03. Observed: C, 58.67; H, 4.02; N, 4.01.

EXAMPLE 27

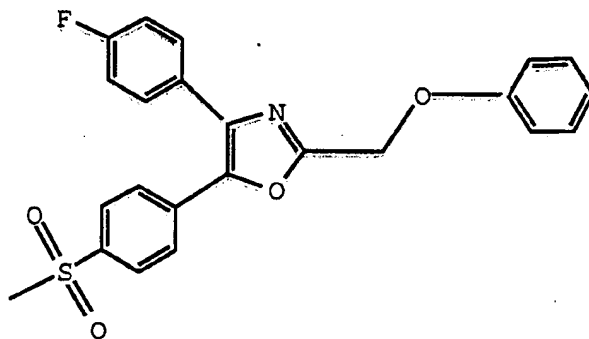
5

4-(4-Fluorophenyl)-2-(2-hydroxyethyl)-5-[4-(methylsulfonyl)phenyl]oxazole

4-(4-Fluorophenyl)-2-(2-hydroxyethyl)-5-[4-(methylsulfonyl)phenyl]oxazole was prepared in a manner consistent with that described in Example 20. The m/z 362 (M+H)⁺ was consistent with the assigned structure.

EXAMPLE 28

15



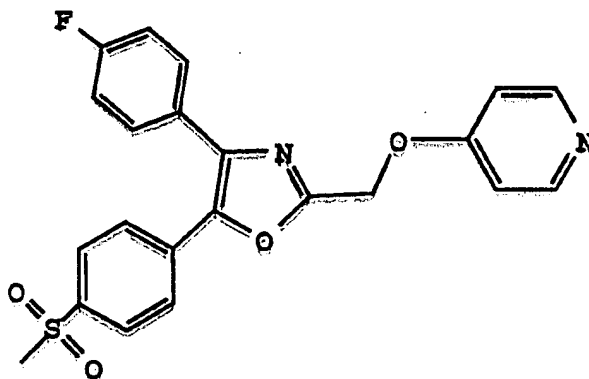
4-(4-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenoxyethyl oxazole

20

A solution containing 1.69 g (4.87 mmol) of 4-(4-fluorophenyl)-2-hydroxymethyl-5-[4-(methylsulfonyl)phenyl]oxazole (Example 26) in 100 mL of methylene chloride was stirred at 25°C as 1.36 mL (9.74 mmol) of triethylamine was added dropwise, followed by

the addition of 560 μ L (7.30 mmol) of methanesulfonyl chloride. The reaction was stirred for 20 minutes, after which the organic solution was washed with 1N HCl, dried over sodium sulfate and concentrated in vacuo to give methyl [4-(4-fluorophenyl)-5-[4-(methanesulfonyl)phenyl]oxazol-2-yl]methanesulfonate as a yellow oil which was characterized as the expected mesylate by its NMR spectrum: $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 3.08 (s, 3H), 3.17 (s, 3H), 5.37 (s, 2H), 7.12 (t, 2H, $J=8.8$ Hz), 7.58 (m, 2H), 7.78 (d, 2H, $J=8.8$ Hz) and 7.94 (d, 2H, $J=8.8$ Hz). This material was used without further purification. A solution containing 544 mg (1.28 mmol) of methyl [4-(4-fluorophenyl)-5-[4-(methanesulfonyl)phenyl]oxazol-2-yl]methanesulfonate in 20 mL of DMF was stirred at 25°C as 353 mg (2.56 mmol) of potassium carbonate and 240 mg (2.56 mmol) of phenol were added. The reaction was stirred for 2 days at 25°C and poured into 100 mL of water. To this mixture was added 100 mL of ethyl acetate and the layers separated. The organic layer was washed with water, dried over sodium sulfate and concentrated in vacuo to give a crude beige solid which was purified by flash chromatography on a silica gel column using 25% ethyl acetate/hexane as the eluent to give 475 mg (88%) of a white solid which was recrystallized from 50% ethyl acetate/isooctane to give a white crystalline solid (mp 168-169°C) whose structure was assigned as 4-(4-fluorophenyl)-5-[4-(methanesulfonyl)-phenyl]-2-phenoxy-methyloxazole on the basis of its spectral characteristics: $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 3.07 (s, 3H), 5.23 (s, 2H), 6.98 (m, 5H), 7.33 (t, 2H, $J=8.2$ Hz), 7.60 (m, 2H), 7.77 (d, 2H, $J=8.5$ Hz) and 7.92 (d, 2H, $J=8.5$ Hz). $^{19}\text{F-NMR}$ (CDCl_3 , 280 MHz) δ -111.9. Analysis calc. for $\text{C}_{23}\text{H}_{18}\text{NO}_4\text{FS}$ - C: 65.24, H: 4.28, 3.31. Observed- C: 65.10, H: 4.29, N: 3.28.

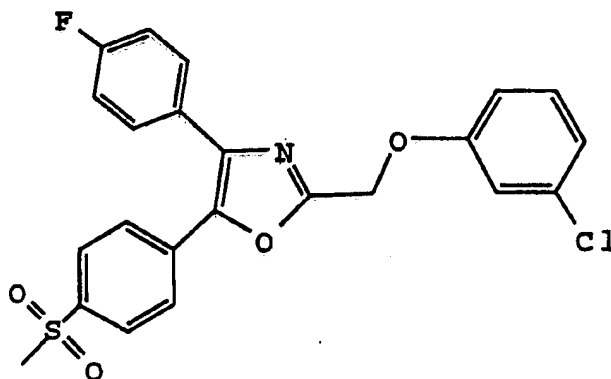
EXAMPLE 29



5 4-(4-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-
2-(pyridyloxymethyl)oxazole

4-(4-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-(pyridyloxymethyl)oxazole was prepared in a manner
10 consistent with Example 28. Melting point: 276-278°C.

EXAMPLE 30



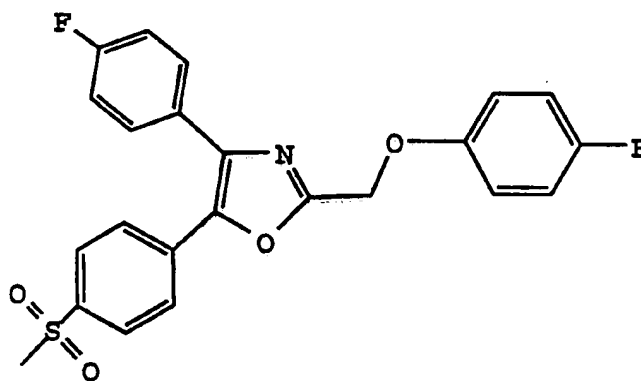
15

2-(3-Chlorophenoxymethyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazole

A solution containing 612 mg (1.44 mmol) of methyl
20 [4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-
2-yl]methanesulfonate (as prepared in Example 28) in 20

mL of DMF was stirred at 25°C as 397 mg (2.88 mmol) of potassium carbonate and 0.3 mL (2.88 mmol) of 3-chlorophenol were added. The reaction was stirred for 2 days at 25°C and poured into 100 mL of water. To this mixture was added 100 mL of ethyl acetate and the layers separated. The organic layer was washed with water, dried over sodium sulfate and concentrated in vacuo to give the crude solid which was purified by flash chromatography on a silica gel column using 50% ethyl acetate/hexane as the eluent to give 528 mg (80%) of a white solid which was recrystallized from 50% dichloromethane/isooctane to give a white crystalline solid (mp 112-114°C) whose structure was assigned as 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-(3-chlorophenoxy)methyloxazole on the basis of its spectral characteristics: ¹H-NMR (CDCl₃, 300 MHz) δ 3.08 (s, 3H), 5.22 (s, 2H), 7.08 (m, 2H), 7.13 (m, 3H), 7.26 (m, 1H), 7.59 (dd, 2H, J=8.8, 5.4 Hz), 7.62 (dd, 2H, J=8.8, 5.4 Hz), 7.78 (d, 2H, J=8.8 Hz), 7.93 (d, 2H, J=8.8 Hz). ¹⁹F-NMR (CDCl₃, 280 MHz) δ -111.8. Analysis Calc'd. for C₂₃H₁₇NO₄FSCl: C, 60.33; H, 3.74; N, 3.06. Observed: C, 60.19; H, 3.80; N, 3.03.

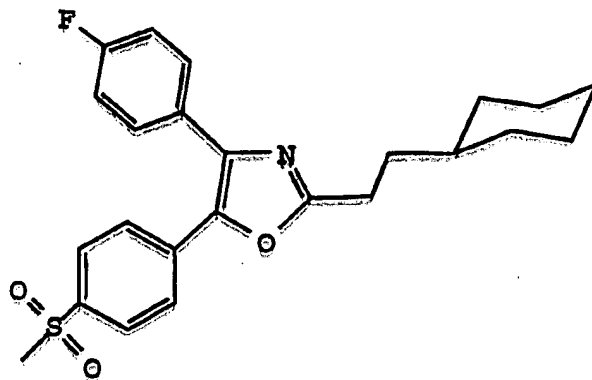
EXAMPLE 31



4-(4-Fluorophenyl)-2-(4-fluorophenoxymethyl)-5-[4-(methylsulfonyl)phenyl]oxazole

A solution containing 585 mg (1.37 mmol) of methyl [4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]methanesulfonate (as prepared in Example 28) in 15 mL of DMF was stirred at 25°C as 380 mg (2.74 mmol) of potassium carbonate and 308 mg (2.74 mmol) of 4-fluorophenol are added. The reaction was stirred for 2 days at 25°C and poured into 100 mL of water. To this mixture was added 100 mL of ethyl acetate and the layers separated. The organic layer was washed with water, dried over sodium sulfate and concentrated in vacuo to give the crude solid which was purified by flash chromatography on a silica gel column using 50% ethyl acetate/hexane as the eluent to give 528 mg (80%) of a white solid which was recrystallized from 50% dichloromethane/isooctane to give a white crystalline solid (mp 133-134°C) whose structure was assigned as 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)-phenyl]-2-[(4-fluorophenoxy)methyl]oxazole on the basis of its spectral characteristics: ¹H-NMR (CDCl₃, 300 MHz) δ 3.08 (s, 3H), 5.19 (s, 2H), 7.00 (m, 4H), 7.13 (m, 2H), 7.58 (dd, 2H, J=8.8, 5.2 Hz), 7.61 (dd, 2H, J=8.8, 5.2 Hz), 7.77 (d, 2H, J=8.7 Hz), 7.93 (d, 2H, J=8.7 Hz). ¹⁹F-NMR (CDCl₃, 280 MHz) δ -111.8, -122.5. Analysis Calc'd. for C₂₃H₁₇NO₄F₂S: C, 62.58; H, 3.88; N, 3.17. Observed: C, 62.44; H, 4.04; N, 3.11.

EXAMPLE 32



5 2-(Cyclohexylethyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazole

A solution containing 2.02 g (7.24 mmol) of 1-(4-fluorophenyl)-2-hydroxy-2-[4-(methylthiophenyl)ethanone
 10 in 100 mL of methylene chloride was stirred at 25°C as 1.76 mL (21.72 mmol) of pyridine was added, followed by the addition of 1.52 g (8.69 mmol) of 2-cyclohexylpropionyl chloride. The reaction was stirred at 25°C for 48 hours, after which the resulting yellow
 15 solution was washed with 1N HCl, dried over sodium sulfate and concentrated in vacuo. The crude solid was purified via flash chromatography on a silica gel column using 10 % ethyl acetate/hexane as the eluent. This provided 2.87 g (96 %) of a white foam, which was
 20 characterized as the benzoin ester on the basis of its NMR spectra: ¹H-NMR (CDCl₃, 300 MHz) δ 0.80-0.96 (m, 2H), 1.10-1.25 (m, 4H), 1.45-1.78 (m, 7H), 2.40 (m, 2H), 2.43 (s, 3H), 6.75 (s, 1H), 7.05 (m, 2H), 7.23 (d, 2H, J=8 Hz), 7.35 (d, 2H, J=8 Hz) and 7.95 (m, 2H). ¹⁹F-NMR (CDCl₃, 280 MHz) δ -104.4.
 25

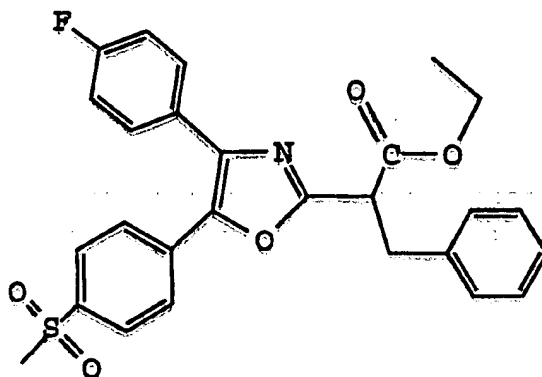
A solution containing 2.87 g (6.92 mmol) of the benzoin ester and 5.3 g (69 mmol) of ammonium acetate in 100 mL of acetic acid was heated to 80°C for 2 hours. The reaction was cooled to 25°C and poured into water.

The product was extracted into ethyl acetate and the combined organic extracts washed with an aqueous solution of sodium bicarbonate. The solution was dried over sodium sulfate and concentrated *in vacuo* to give the crude oxazole. This crude material was purified by flash chromatography on a silica gel column using 25% ethyl acetate/hexane as the eluent to give 1.87 g (68%) of a clear oil, which was characterized as 2-(2-cyclohexylethyl)-4-(4-fluorophenyl)-5-[4-(methythio)phenyl]oxazole on the basis of its spectral properties: $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 0.90-1.02 (m, 2H), 1.10-1.40 (m, 4H), 1.62-1.82 (m, 7H), 2.49 (s, 3H), 2.84 (t, $J=2.0$ Hz, 2H), 7.03 (d, $J=8.7$ Hz, 1H), 7.06 (d, $J=8.7$ Hz, 1H), 7.22 (d, $J=8.6$ Hz, 2H), 7.45 (d, $J=8.6$ Hz, 2H), 7.58 (d, $J=5.4$ Hz, 1H), 7.61 (d, $J=5.4$ Hz, 1H). The material from this experiment was used directly in the next step without further purification.

A solution of 1.87g (4.73 mmol) of 2-(2-cyclohexylethyl)-4-(4-fluorophenyl)-5-[4-(methythio)phenyl]oxazole in 100 mL of methylene chloride was stirred at -78°C as 3.26 g (9.46 mmol based on 50% purity) of *m*-chloroperoxybenzoic acid was added all at once. The reaction was stirred at -78°C for 1 hour and TLC (silica, 50% hexane/ethyl acetate) indicated that the reaction mixture consisted of mostly sulfone. The reaction was poured into a solution of aqueous sodium metabisulfite. The aqueous solution was extracted using ethyl acetate and the organic layer was washed with saturated sodium metabisulfite, saturated sodium bicarbonate and brine. The resulting clear solution was dried over sodium sulfate and concentrated *in vacuo* to give a white solid which was purified by flash chromatography on a silica gel column using 50% ethyl acetate/hexane as the eluent. Recrystallization from 50% ethyl acetate/isooctane gave 1.76 g (87%) of a low melting semi-solid whose structure was assigned as 2-(2-cyclohexylethyl)-4-(4-fluorophenyl)-5-[4-

(methylsulfonyl)phenyl]oxazole on the basis of its spectral characteristics: $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 0.90-1.06 (m, 2H), 1.11-1.40 (m, 7H), 2.87 (apparent t, $J=8.1\text{Hz}$, 2H), 3.07 (s, 3H), 7.10 (t, $J=8.7\text{Hz}$, 2H), 7.59 (m, 2H), 7.74 (d, $J=8.7\text{Hz}$, 2H), 7.90 (d, $J=8.7\text{Hz}$, 2H). $^{19}\text{F-NMR}$ (CDCl_3 , 280 MHz) δ -112.49. LRMS m/z 427 (M)+. HRMS Calc'd. for $\text{C}_{24}\text{H}_{26}\text{NO}_3\text{FS}$: 421.1617. Observed: 421.1611. Analysis Calc'd. for $\text{C}_{24}\text{H}_{26}\text{NO}_3\text{FS}$: C, 67.43; H, 6.13; N, 3.28. Observed: C, 67.27; H, 6.15; N, 3.24.

EXAMPLE 33



Ethyl 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-oxazolyl]-2-benzyl-acetate

Step 1: Preparation of 2-(4-fluorophenyl)-3-(4-methylthiophenyl)propenoic acid

Acetic anhydride (500 mL), 4-(methylthio)benzaldehyde (100.2 g, 0.66 mol), 4-fluorophenylacetic acid (101.6 g, 0.66 mol), and triethylamine (68.1 g, 0.67 mol) were placed in a 3 L round bottom flask and heated to reflux for 1.75 hours. The reaction was cooled to 110°C , and water (500 mL) was added cautiously through an addition funnel. This caused the solution to reflux vigorously and the temperature to rise to 135°C . A yellow precipitate

formed, and after cooling to room temperature, was collected by filtration, washed with water, and recrystallized from ethyl acetate/isooctane to provide the diarylacrylic acid as yellow needles (135.2 g, 71%):
5 mp 172-176°C. ¹H NMR (acetone d₆) 300 MHz 7.84 (s, 1H), 7.03-7.28 (m, 10H), 2.46 (s, 3H). ¹⁹F NMR (acetone d₆) -116.11 (m). Mass spectrum M⁺ 288.

10 Step 2: Preparation of 1-(4-fluorophenyl)-2-(4-methylthiophenyl)ethanone

The diaryl acrylic acid (226.5 g, 0.78 mol) was placed in a 2 L round bottom flask with anhydrous toluene (800 mL) and triethylamine (81.2 g, 0.80 mol). After cooling to 0°C, diphenylphosphoryl azide (217.4 g,
15 0.79 mol) was added, the solution was stirred at 0°C for 20 minutes and at room temperature for 2.50 hours. The reaction was poured into water, extracted with ether, dried over magnesium sulfate, and concentrated in vacuo to remove the ether. The remaining toluene solution was
20 heated to reflux and a vigorous evolution of gas occurred. After 1.25 hours, tert-butyl alcohol (80 mL, 0.84 mol) was added to the reaction. After an additional 20 minutes, concentrated hydrochloric acid (41 mL) was added slowly causing the reaction to foam.
25 The reaction was heated at 90°C overnight (14 hours) and a white precipitate formed after cooling. The precipitate was isolated by filtration, washed with cold ether, and air dried to yield the desired intermediate (182.7 g, 89%): mp 134.5-138°C. ¹H NMR (acetone d₆) 300
30 MHz 8.16 (m, 2H), 7.24 (m, 6H), 4.34 (s, 2H), 2.46 (s, 3H). ¹⁹F NMR (acetone d₆) -107.88 (m).

Step 3: Preparation of 1-(4-fluorophenyl)-2-(4-methylthiophenyl)-2-hydroxy-ethanone

35 A 1 L three necked round bottomed flask equipped with reflux condenser, magnetic stir bar, thermometer adapter, and constant pressure addition funnel was

charged with the intermediate from Step 2, (55.5 g, 0.21 mol), acetic acid (250 mL) and 33% HBr in acetic acid (120 mL). The solution was stirred and treated with bromine (11.1 mL, 0.21 mol) from the addition funnel at such a rate that the bromine color was discharged rapidly, ca. 15 minutes. After an additional 10 minutes at room temperature, the solution was filtered through a Buchner funnel and the filtrate concentrated *in vacuo* to give an orange solid. The crude bromoketone was dissolved in dichloromethane and washed with 1N NaHSO₃, dried over anhydrous MgSO₄, filtered and concentrated *in vacuo* to give 68.8 g of 1-(4-fluorophenyl)-2-(4-methylthiophenyl)-2-bromoethanone as a yellow solid which was used directly without further purification. The crude bromoketone was dissolved in 300 mL acetone and 150 mL of water and heated to reflux for 2.5 hours. The solution was concentrated *in vacuo* and the residue taken up in dichloromethane, washed with saturated aqueous sodium bicarbonate, brine, dried over anhydrous magnesium sulfate, filtered and reconcentrated *in vacuo* to give a light yellow solid that was crystallized from a mixture of dichloromethane and isooctane to provide 37.8 g (65%) of pure 1-(4-fluorophenyl)-2-(4-methylthiophenyl)-2-hydroxy-ethanone: mp 90-92 °C.

Step 4: Preparation of ethyl 2-[4-(4-fluorophenyl)-5-[4-methylthio)phenyl]]-2-oxazoleacetate

A solution containing 8.00 g (29 mmol) of 1-(4-fluorophenyl)-2-hydroxy-2-[4-(methylthiophenyl)ethanone in 100 mL of methylene chloride was stirred at 25°C as 7.0 mL (31 mmol) of pyridine was added, followed by the addition of 4.5 mL (35 mmol) of ethyl malonyl chloride. The reaction was stirred at 25°C for 48 hours, after which the resulting yellow solution was washed with 1N HCl, dried over sodium sulfate and concentrated *in vacuo*. The crude solid was purified via flash chromatography on a silica gel column using 10% ethyl

100

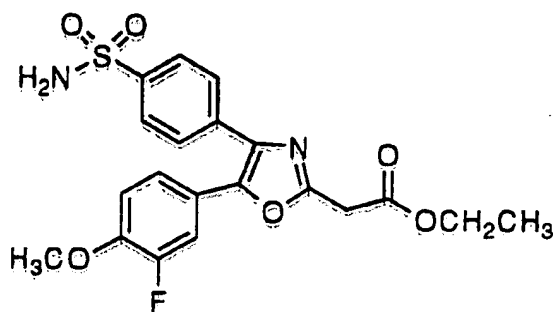
acetate/hexane as the eluent. This provided 7.31 g (64%) of a white foam, which was used directly without further purification. The product from above (7.31 g, 18.7 mmol) and 7.2 g of ammonium acetate (93.5 mmol, 5 equivalents) in 50 mL of glacial acetic were heated to reflux for 2 hours. The reaction mixture was cooled to 25°C and poured into 100 mL of water. The aqueous solution was extracted with ethyl acetate and the combined organic extracts were washed with water and sodium bicarbonate solution, dried over sodium sulfate and concentrated *in vacuo*. The crude solid was purified by flash chromatography using a silica gel column and 20% ethyl acetate/hexane as the eluent to give a white solid which was recrystallized from 50% ethyl acetate/isooctane to give 5.55 g (80%) of a white solid whose structure was assigned as ethyl 2-[4-(4-fluorophenyl)-5-[4-methylthio)phenyl]oxazol-2-yl]acetate and was judged suitable for taking onto the next step.

Step 5: Preparation of ethyl 2-[4-(4-fluorophenyl)-5-[4-methylsulfonyl]phenyl]-2-oxazolyl]-2-benzyl-acetate

A solution of 755 mg (2.03 mmol) of ethyl 2-[4-(4-fluorophenyl)-5-[4-methylthio]phenyl]oxazol-2-yl]acetate (from Step 4) was dissolved in 20 mL of anhydrous tetrahydrofuran (THF) and cooled to -78°C and treated with a solution of potassium bis(trimethylsilyl)amide (2.44 mL, 1.2 equivalents, 1M in THF via syringe). The solution was maintained at -78°C for 15 minutes and treated with a solution of 290 μ L (2.44 mmol) of benzyl bromide. The solution was warmed to room temperature and poured into a saturated aqueous solution of ammonium chloride. The aqueous solution was extracted with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give an oil that was purified by flash chromatography on silica gel eluting with 10% ethyl acetate/hexane to provide 396 mg of the dialkylated product and 182 mg (19%) of ethyl 2-[4-(4-fluorophenyl)-5-[4-methylthio]phenyl]oxazol-2-yl]-1-benzyl-acetate that was used directly in the next step. A solution of 182 mg (0.344 mmol) of ethyl 2-[4-(4-fluorophenyl)-5-[4-methylthio]phenyl]oxazol-2-yl]-1-benzyl-acetate in 5 mL of dichloromethane was cooled to -78°C and treated with 272 mg (2 equivalents) of *m*-chloroperoxybenzoic acid for 2 hours. The reaction was poured into a solution of aqueous sodium metabisulfite. The aqueous solution was extracted using ethyl acetate and the organic layer was washed with saturated sodium metabisulfite, saturated sodium bicarbonate and brine. The resulting clear solution was dried over sodium sulfate and concentrated in vacuo to give a transparent oil which was purified by flash chromatography on a silica gel column using 30% ethyl acetate/hexane as the eluent. The purified material was an oil whose structure was assigned as ethyl 2-[4-(4-fluorophenyl)-5-[4-methylsulfonyl]phenyl]oxazol-2-yl]-2-benzyl-acetate on the basis of its spectral characteristics: $^1\text{H-NMR}$

(CDCl₃, 300 MHz) δ 1.20 (t, J= 7.0Hz, 3H), 3.07 (s, 3H), 3.53 (m, 2H), 4.19 (q, J= 7.0Hz, 2H), 4.23 (m, 1H), 7.10 (d, J= 8.7Hz, 2H), 7.25 (m, 5H), 7.57 (m, 2H), 7.70 (d, J= 8.7Hz, 2H), 7.90 (d, J= 8.7Hz, 2H). ¹⁹F-NMR (CDCl₃, 280 MHz) δ -112.15. LRMS m/z 493 (M)⁺, HRMS Calc'd. for C₂₇H₂₄NO₅FS: 493.1359. Observed: 493.1371.

EXAMPLE 34



Ethyl [4-(4-aminosulfonylphenyl)-5-(3-fluoro-4-methoxyphenyl)]-2-oxazoleacetate

15 Step 1. Preparation of 2-hydroxy-2-(3-fluoro-4-methoxyphenyl)-1-phenylethanone

A solution of 3-fluoro-para-anisaldehyde (25.00 g, 162 mmol) and zinc iodide (0.27 g) in dichloromethane (100 mL) was treated with a solution of trimethylsilylcyanide (22 mL, 165 mmol) in dichloromethane (20 mL). The solution was stirred for 0.4 hours at room temperature, washed with saturated NaHCO₃, dried over MgSO₄, and concentrated *in vacuo* to give the trimethylsilyl cyanohydrin as an orange oil (37.83 g). The trimethylsilyl-cyanohydrin was dissolved in diethyl ether (50 mL) and added dropwise to a solution of phenylmagnesium bromide (174 mmol) in diethyl ether (658 mL) while maintaining the temperature between 25-35 °C with an ice water bath. The reaction was stirred for 0.4 hours at room temperature then quenched by adding 3N HCl. The

reaction mixture was extracted with ethyl acetate, washed with saturated NaHCO_3 and brine, dried over MgSO_4 , and concentrated in vacuo to give an orange oil (39.57 g). The orange oil was dissolved in 9:1 trifluoroacetic acid/water (80 mL) and stirred for 1.4 hours at room temperature. The reaction was neutralized with solid sodium carbonate, extracted with ethyl acetate, washed with 10% Na_2CO_3 and brine, dried over MgSO_4 , and concentrated in vacuo to give a brown solid which was recrystallized from diethyl ether/hexane to give the benzoin (13.87 g, 33%): mp 76-79 °C. ^1H NMR (CDCl_3) 300 MHz δ 7.89 (d, $J=7.3$ Hz, 2H) 7.55 (m, 1H) 7.42 (m, 2H) 7.05 (m, 2H) 6.90 (m, 1H) 5.88 (br d, $J=3.0$ Hz, 1H) 4.50 (br d, 1H), ^{19}F NMR (CDCl_3) 282 MHz -134.05 (m).

15 Step 2. Esterification of 2-hydroxy-2-(3-fluoro-4-methoxyphenyl)-1-phenylethanone

A solution of benzoin from Step 1 (3.25 g, 12.5 mmol), pyridine (4.94 g, 62.5 mmol), and ethyl malonyl chloride (2.38 g, 15.8 mmol) in dichloromethane (20 mL) was stirred for 94 hours at room temperature. The reaction mixture was washed with 3N HCl, saturated NaHCO_3 and water, dried over MgSO_4 , concentrated in vacuo and passed through a column of silica gel eluting with 25% ethyl acetate/hexane to give a yellow oil (1.93 g, 41%): ^1H NMR (CDCl_3) 300 MHz δ 7.89 (d, $J=7.7$ Hz, 2H) 7.53 (m, 1H) 7.41 (m, 2H) 7.16 (m, 2H) 6.92 (m, 1H) 6.84 (s, 1H) 4.50 (q, $J=7.0$ Hz, 2H) 3.85 (d, $J=1.0$ Hz, 3H) 3.52 (s, 2H) 1.25 (t, $J=7.0$ Hz, 3H). ^{19}F NMR (CDCl_3) 282 MHz -133.67 (m). Mass spectrum: $M+\text{Li}=381$.

30 Step 3. Preparation of ethyl [4-phenyl-5-(3-fluoro-4-methoxyphenyl)]-2-oxazoleacetate.

The ketone from the Step 2 (1.83 g, 4.9 mmol) was dissolved in acetic acid (25 mL), treated with ammonium acetate (3.86 g, 50.0 mmol), and heated to reflux for 2.0 hours. The reaction mixture was diluted with ethyl acetate,

washed with water, saturated NaHCO_3 , and brine, dried over MgSO_4 , concentrated *in vacuo*, and passed through a column of silica gel eluting with 16% ethyl acetate/hexane to give a yellow solid (0.67 g, 39%); mp 85-86 °C. ^1H NMR (CDCl_3) 300 MHz δ 7.61 (d, $J=7.5$ Hz, 2H) 7.35 (m, 5H) 6.93 (m, 1H) 4.24 (q, $J=7.1$ Hz, 2H) 3.93 (s, 2H) 3.91 (s, 3H) 1.30 (t, $J=7.1$ Hz, 3H). ^{19}F NMR (CDCl_3) 282 MHz δ 134.77 (m). High resolution mass spectrum Calc'd. for $\text{C}_{20}\text{H}_{18}\text{FNO}_4$: 356.1298. Found: 356.1303.

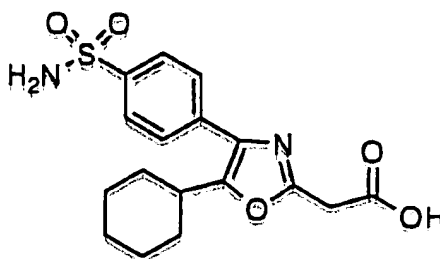
10

Step 4. Preparation of ethyl [4-(4-aminosulfonylphenyl)-5-(3-fluoro-4-methoxyphenyl)]-2-oxazoleacetate

The compound from Step 3 (0.63 g, 1.8 mmol) was stirred with chlorosulfonic acid (15 mL) for 1.1 hours at 5 °C. The reaction mixture was slowly added to ice water, and extracted with dichloromethane. The dichloromethane solution was stirred at 5 °C with ammonium hydroxide for 3.0 hours. The organic layer was collected, washed with 3N HCl, dried over MgSO_4 , concentrated *in vacuo*, and the residue recrystallized from ethyl acetate/hexane to give a white solid (0.02 g, 2.6%); mp 127-130 °C. ^1H NMR (acetone- d_6) 300 MHz δ 7.90 (d, $J=8.7$ Hz, 2H) 7.84 (d, $J=8.7$ Hz, 2H) 7.38 (m, 2H) 7.26 (m, 1H) 6.64 (br s, 1H) 4.20 (q, $J=7.0$ Hz, 2H) 4.01 (s, 2H) 3.95 (s, 3H) 1.27 (t, $J=7.0$ Hz, 3H). ^{19}F NMR (acetone- d_6) 282 MHz -135.76 (m). High resolution mass spectrum Calc'd. for $\text{C}_{20}\text{H}_{20}\text{F}_2\text{N}_2\text{O}_6\text{S}$: 435.1026. Found: 435.1036.

25

EXAMPLE 35



5 [4-(4-Aminosulfonylphenyl)-5-cyclohexyl]-2-oxazoleacetic acid

Step 1. Preparation of 2-hydroxy-2-cyclohexyl-1-phenylethanone

10 A solution of cyclohexanecarboxaldehyde (8.5 g, 76 mmol) and zinc iodide (0.11 g) in dichloromethane (40 mL) was treated with a solution of trimethylsilylcyanide (10 mL, 76 mmol) in dichloromethane (20 mL). The solution was stirred for 0.33 hours at room temperature, washed with water and

15 saturated NaHCO₃, dried over MgSO₄, and concentrated in *vacuo* to give the trimethylsilyl cyanohydrin as an orange oil (13.02 g). The trimethylsilyl cyanohydrin was dissolved in diethyl ether (50 mL) and added dropwise to a solution of phenylmagnesium bromide (54 mmol) in diethyl ether (268 mL)

20 while maintaining the temperature between 25-35 °C with an ice water bath. The reaction was stirred for 0.67 hours at room temperature then quenched by adding 3N HCl (60 mL). The organic layer was collected, washed with saturated NaHCO₃ and brine, dried over MgSO₄, and concentrated in *vacuo* to give a

25 white solid (12.96 g). The white solid was dissolved in 9:1 trifluoroacetic acid/water (50 mL) and stirred for 2.0 hours at room temperature. The reaction was neutralized with solid sodium carbonate, extracted with ethyl acetate, washed with saturated NaHCO₃ and brine, dried over MgSO₄, concentrated in

vacuo and recrystallized from diethyl ether/hexane to give the benzoin (2.55 g, 25%): mp 87-92 °C. ¹H NMR (CDCl₃) 300 MHz δ 7.88 (d, J=7.1 Hz, 2H) 7.62 (m, 1H) 7.50 (m, 2H) 4.93 (d, J=2.2 Hz 1H) 3.60 (br s, 1H) 1.52-1.82 (m, 6H) 1.02 1.24 (m, 5H). Mass spectrum: M+Li=225.

Step 2. Esterification of 2-hydroxy-2-cyclohexyl-1-phenylethanone

The ethanone of Step 1 (2.55 g, 11.7 mmol) was dissolved in THF (10 mL), 2,2-dimethyl-1,3-dioxane-4,6-dione (1.73 g, 12.0 mmol) was added and the reaction was heated to reflux for 17.3 hours. The reaction mixture was partitioned between saturated NaHCO₃ and diethyl ether. The aqueous layer was acidified with concentrated HCl, extracted with diethyl ether, washed with brine, dried over MgSO₄, and concentrated in vacuo to give a yellow oil (2.26 g) which was used in the next step without further purification.

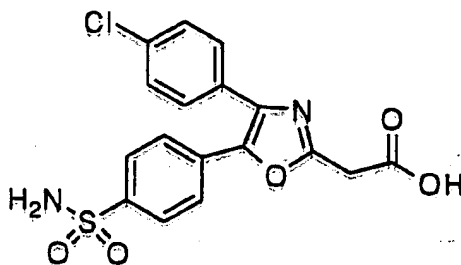
Step 3. Preparation of 2-carboxymethyl-4-hydroxy-4-phenyl-5-cyclohexyloxazoline

The ethanone from the Step 2 (1.87 g, 6.1 mmol) was dissolved in ethanol (20 mL), treated with ammonium acetate (4.94 g, 16.3 mmol), and heated to reflux for 4.3 hours. The reaction mixture was concentrated in vacuo, and the residue was partitioned between saturated NaHCO₃ and ethyl acetate. The aqueous layer was acidified with 3N HCl, extracted with diethyl ether, washed with brine, dried over MgSO₄, and concentrated in vacuo dissolved in ethyl acetate, washed with water, saturated NaHCO₃, and brine, dried over MgSO₄, and concentrated in vacuo to give a white solid (0.75 g, 43%): mp 151-155 °C dec. Mass spectrum: M+Li=310.

Step 4. Preparation of [4-(4-aminosulfonylphenyl)-5-cyclohexyl]-2-oxazoleacetic acid

The compound from Step 3 (0.47 g, 1.6 mmol) was stirred with chlorosulfonic acid (2.5 mL) for 1.25 hours at 5 °C. The reaction mixture was slowly added to ice water, and extracted with dichloromethane. The dichloromethane was stirred at room temperature with ammonium hydroxide (20 mL) for 23.1 hours. The aqueous layer was collected, acidified with concentrated HCl, and filtered to give a white solid (0.17 g, 28%): mp 223-230 °C, ¹H NMR (acetone-d₆) 300 MHz δ 7.95 (d, 2H) 7.85 (d, 2H) 6.60 (br s, 2H) 3.90 (s, 2H) 3.20 (m, 1H) 1.20-1.95 (m, 10H). High resolution mass spectrum Calc'd. for C₁₇H₂₁N₂O₅S: 365.1171. Found: 365.1187.

EXAMPLE 36



[5-(4-Aminosulfonylphenyl)-4-(4-chlorophenyl)]-2-oxazoleacetic acid

20 Step 1. Preparation of 2-hydroxy-2-phenyl-1-(4-chlorophenyl)ethanone

The trimethylsilyl cyanohydrin of benzaldehyde, prepared similar to that described in Example 34, Step 1, (10.18 g, 50 mmol) was dissolved in diethyl ether (10 mL) and added dropwise to a solution of 4-chlorophenylmagnesium bromide (59 mmol) in diethyl ether (319 mL) while maintaining the temperature between 23-35 °C with an ice water bath. The reaction was stirred for 1.2 hours at room temperature then quenched by adding 3N HCl (50 mL). The organic layer was collected, washed with saturated NaHCO₃ and brine, dried over

MgSO₄, and concentrated *in vacuo* to give a yellow oil (15.57 g). The yellow oil was dissolved in 9:1 trifluoroacetic acid/water (30 mL) and stirred for 1.75 hours at room temperature. The reaction was neutralized with solid sodium carbonate, extracted with ethyl acetate, washed with 10% Na₂CO₃ and brine, dried over MgSO₄, concentrated *in vacuo* and recrystallized from diethyl ether/hexane to give the benzoin (5.76 g, 47%): mp 87-92 °C.

10 Step 2. Esterification of 2-hydroxy-2-phenyl-1-(4-chlorophenyl)ethanone

The ethanone from Step 1 (4.28 g, 17.3 mmol) was dissolved in THF (15 mL), 2,2 dimethyl-1,3-dioxane-4,6-dione (2.52 g, 17.5 mmol) was added and the reaction heated to reflux for 15.7 hours. The reaction mixture was partitioned between saturated NaHCO₃ and diethyl ether. The aqueous layer was acidified with concentrated HCl, extracted with diethyl ether, washed with brine, dried over MgSO₄, and concentrated *in vacuo* to give a yellow oil (4.55 g) which was used in the next step without further purification: Mass spectrum: M+Li=339.

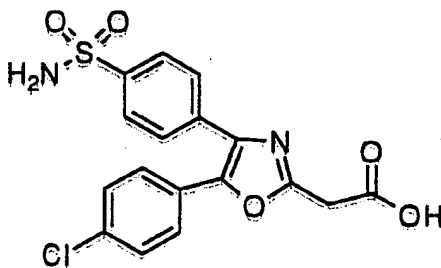
Step 3. Preparation of [4-(4-chlorophenyl)-5-phenyl]-2-oxazoleacetic acid

25 The ester from Step 2 (4.69 g, 14.1 mmol) was dissolved in ethanol (20 mL), treated with ammonium acetate (10.87 g, 141.0 mmol), and heated to reflux for 4.75 hours. The ethanol was removed *in vacuo* and the residue was dissolved in water, acidified with 3N HCl, precipitated with diethyl ether and hexane and filtered to give an orange solid (2.71 g, 61%): mp 158-160 °C. ¹H NMR (DMSO-d₆) 300 MHz δ 14.8 (br s, 1H) 7.48 (m, 9H) 4.19 (s, 2H).

35 Step 4. Preparation of [5-(4-aminosulfonylphenyl)-4-(4-chlorophenyl)]-2-oxazoleacetic acid

The compound from Step 3 (1.71g, 5.4 mmol) was stirred with chlorosulfonic acid (7 mL) for 1.25 hours at 5 °C. The reaction mixture was added to ice water, and extracted with dichloromethane. The dichloromethane was stirred with ammonium hydroxide (30 mL) for 1.2 hours at room temperature. The aqueous layer was collected and acidified with concentrated HCl, extracted with ethyl acetate, dried over MgSO₄, and concentrated *in vacuo* to give a white solid (0.11 g, 5%): ¹H NMR (DMSO-d₆) 300 MHz δ 13.5 (br s, 1H) 7.81 (d, J=8.5 Hz, 2H) 7.62 (d, J=8.3 Hz, 2H) 7.47 (m, 6H) 3.90 (s, 2H).

EXAMPLE 37



[4-(4-Aminosulfonylphenyl)-5-(4-chlorophenyl)]-2-oxazoleacetic acid

20 Step 1. Preparation of 2-hydroxy-2-(4-chlorophenyl)-1-phenylethanone.

A solution of 4-chlorobenzaldehyde (9.86 g, 70 mmol) and zinc iodide (0.18 g) in dichloromethane (40 mL) was treated with a solution of trimethylsilylcyanide (9 mL, 71 mmol) in dichloromethane (20 mL). The solution was stirred for 0.33 hours at room temperature, washed with water and saturated NaHCO₃, dried over MgSO₄, and concentrated *in vacuo* to give the trimethylsilyl cyanohydrin as an orange oil (13.90 g). The trimethylsilyl cyanohydrin was dissolved in diethyl ether (50 mL) and added dropwise to a solution of phenylmagnesium

bromide (69 mmol) in diethyl ether (269 mL) while maintaining the temperature between 15-28 °C with an ice water bath. The reaction was stirred for 0.75 hours at room temperature then quenched by adding 3N HCl (50 mL). The organic layer was collected, washed with saturated NaHCO₃ and brine, dried over MgSO₄, and concentrated in vacuo to give a yellow solid (13.06 g). The yellow solid was dissolved in 9:1 trifluoroacetic acid/water (30 mL) and stirred for 1.6 hours at room temperature. The reaction was neutralized with solid sodium carbonate, extracted with ethyl acetate, washed with 10% Na₂CO₃ and brine, dried over MgSO₄, concentrated in vacuo to give a yellow solid (9.43 g) and used in the next step without further purification.

15 Step 2. Esterification of 2-hydroxy-2-(4-chlorophenyl)-1-phenylethanone

The ethanone from Step 1 (4.34 g, 17.6 mmol) was dissolved in THF (40 mL), 2,2 dimethyl-1,3-dioxane-4,6-dione (2.56 g, 17.8 mmol) was added and the reaction heated to reflux for 18.3 hours. The reaction mixture was partitioned between saturated NaHCO₃ and diethyl ether. The aqueous layer was acidified with concentrated HCl, extracted with diethyl ether, washed with brine, dried over MgSO₄, and concentrated in vacuo to give a yellow oil (4.66 g, 68%): ¹H NMR (CDCl₃) 300 MHz δ 7.89 (d, J=8.5 Hz, 2H) 7.54 (m, 1H) 7.35 (m, 6H) 6.90 (s, 1H) 3.59 (s, 2H). Mass spectrum M+Li=339.

25 Step 3. Preparation of [5-(4-chlorophenyl)-4-phenyl]-2-oxazoleacetic acid

30 The ester from Step 2 (2.88 g, 12.4 mmol) was dissolved in ethanol (20 mL), treated with ammonium acetate (6.74 g, 87.4 mmol), and heated to reflux for 4.1 hours. The reaction mixture was concentrated in vacuo, and the residue was partitioned between water and diethyl ether. The aqueous layer was acidified with 3N HCl, allowed stand at room

35

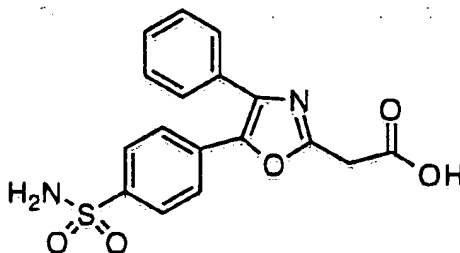
111

temperature then filtered to give a white solid (0.75 g, 28%): mp 217.5-219 °C. Mass spectrum: M+=313.

5 Step 4. Preparation of [4-(4-aminosulfonylphenyl)-5-(4-chlorophenyl)]-2-oxazoleacetic acid

The compound from Step 3 (0.71 g, 2.3 mmol) was stirred with chlorosulfonic acid (7 mL) at 5 °C for 1.0 hour. The reaction mixture was added to ice water, and extracted with dichloromethane. The dichloromethane was stirred with
10 ammonium hydroxide for 1.3 hours at room temperature. The aqueous layer was collected and acidified with concentrated HCl, extracted with ethyl acetate, dried over MgSO₄, and concentrated in vacuo to give a white solid (0.18 g, 20%): mp 118-120 °C (dec). ¹H NMR (DMSO-d₆) 300 MHz δ 7.86 (d, J=8.3
15 Hz, 2H) 7.66 (d, J=8.5 Hz, 2H) 7.56 (m, 4H) 4.15 (s, 2H).

EXAMPLE 38



20 **[5-(4-Aminosulfonylphenyl)-4-phenyl]-2-oxazoleacetic acid**

Step 1. Esterification of benzoin

25 Benzoin (33.32 g, 157 mmol) was dissolved in THF (65 mL), 2,2-dimethyl-1,3-dioxane-4,6-dione (22.85 g, 159 mmol) was added and the reaction heated to reflux for 22.6 hours. The reaction mixture was partitioned between saturated NaHCO₃ and ethyl acetate. The aqueous layer was acidified with
30 concentrated HCl, extracted with diethyl ether, dried over

MgSO₄, and concentrated in vacuo to give a yellow oil (35.08 g) which was used in the next step without further purification.

5 Step 2. Preparation of ethyl [4-hydroxy-4,5-diphenyl-2-oxazolinyl]acetate.

The compound from Step 1 (2.26 g, 7.6 mmol) was dissolved in methanol (25 mL), treated with ammonium acetate (1.26 g, 16.3 mmol), and heated to reflux. After 1.8 hours, 10 the reaction was cooled, acidified by adding concentrated sulfuric acid and heated to reflux for an additional 2.0 hours. The reaction mixture was concentrated in vacuo, and the residue was dissolved in ethyl acetate, washed with water, saturated NaHCO₃, and brine, dried over MgSO₄, and 15 concentrated in vacuo to give an orange oil (1.50 g) which was used in the next step without further purification.

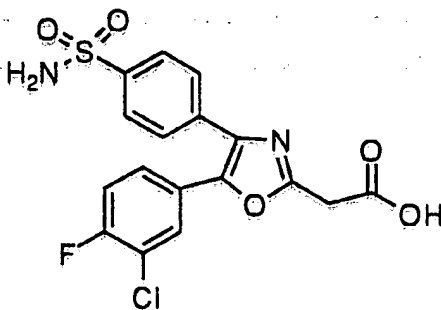
Step 3. Preparation of ethyl [5-(4-aminosulfonylphenyl)-4-phenyl]-2-oxazoleacetate.

20 The compound from Step 2 (1.32 g, 4.2 mmol) was stirred with chlorosulfonic acid (13 mL) for 1.25 hours at 5 °C. The reaction mixture was slowly added to ice water, and extracted with dichloromethane. The dichloromethane was stirred with ammonium hydroxide (40 mL) for 1.9 hours at 5 °C. The 25 organic layer was collected, washed with 3N HCl, dried over MgSO₄, concentrated in vacuo, and passed through a column of silica gel eluting with 40% ethyl acetate/hexane to give a white solid (0.30 g, 19%): mp 84-88 °C. ¹H NMR (acetone-d₆) 300 MHz δ 7.92 (d, J=8.5 Hz, 2H) 7.77 (d, J=8.5 Hz, 2H) 7.63 (m, 2H) 7.41 (m, 3H) 6.71 (br s, 2H) 4.06 (s, 2H) 3.74 (s, 3H). High resolution mass spectrum Calc'd. for C₁₈H₁₇N₂O₅S: 373.0858. Found: 373.0833.

35 Step 4. Preparation of [5-(4-aminosulfonylphenyl)-4-phenyl]-2-oxazoleacetic acid

The oxazole ester from Step 3 (0.65 g, 1.7 mmol) was dissolved in methanol (10 mL), treated with NaOH (0.09 g dissolved in 5 mL water, 2.2 mmol), and stirred at room temperature. After 0.33 hours, additional NaOH (0.10 g, 2.5 mmol) was added and stirring continued for 0.4 hours. Water was added and the reaction mixture was extracted with ethyl acetate. The aqueous layer was acidified with concentrated HCl and extracted with ethyl acetate. The ethyl acetate was washed with brine, dried over MgSO₄, and concentrated in vacuo to give a yellow solid (0.43 g, 69%); mp 134-137 °C (dec). ¹H NMR (acetone-d₆) 300 MHz δ 7.92 (d, J=8.5 Hz, 2H) 7.78 (d, J=8.7 Hz, 2H) 7.64 (m, 2H) 7.42 (m, 3H) 6.68 (br s, 1H) 4.03 (s, 2H). High resolution mass spectrum Calc'd. for C₁₇H₁₅N₂O₅S: 359.0702. Found: 359.0722.

EXAMPLE 39



[4-(4-Aminosulfonylphenyl)-5-(3-chloro-4-fluorophenyl)]-2-oxazoleacetic acid

Step 1. Preparation of 2-hydroxy-2-(3-chloro-4-fluorophenyl)-1-phenylethanone.

A solution of 3-chloro-4-fluorobenzaldehyde (14.00 g, 89 mmol) and zinc iodide (0.16 g) in dichloromethane (50 mL) was treated with a solution of trimethylsilylcyanide (12 mL, 90 mmol) in dichloromethane (15 mL). The solution was stirred for 0.5 hours at room temperature, washed with saturated

NaHCO₃ and brine, dried over MgSO₄, and concentrated in vacuo to give the trimethylsilyl cyanohydrin as an orange oil (20.18 g). The trimethylsilyl cyanohydrin was dissolved in diethyl ether (20 mL) and added dropwise to a solution of phenylmagnesium bromide (90 mmol) in diethyl ether (200 mL) while maintaining the temperature between 25-33 °C with an ice water bath. The reaction was stirred for 0.6 hours at room temperature then quenched by adding 3N HCl (90 mL). The organic layer was collected, washed with saturated NaHCO₃ and brine, dried over MgSO₄, and concentrated in vacuo to give the an orange oil (24.13 g). The orange oil was dissolved in 9:1 trifluoroacetic acid/water (100 mL) and stirred for 1.5 hours at room temperature. The reaction was neutralized with solid sodium carbonate, extracted with diethyl ether, washed with saturated NaHCO₃ and brine, dried over MgSO₄, and concentrated in vacuo to give a brown solid which was recrystallized from diethyl ether/hexane to give the benzoin (9.78 g, 41%): mp 58-63 °C. ¹H NMR (CDCl₃) 300 MHz δ 7.88 (d, J=7.0 Hz, 2H) 7.57 (m, 1H) 7.44 (m, 3H) 7.20 (m, 1H) 7.08 (t, J=8.7 Hz, 1H) 5.92 (s, 1H) 4.60 (br s, 1H). ¹⁹F NMR (CDCl₃) 282 MHz -115.88 (m).

Step 2. Esterification of 2-hydroxy-2-(3-chloro-4-fluorophenyl)ethanone

The ketone from Step 1 (5.54 g, 20.9 mmol) was dissolved in THF (5 mL), 2,2 dimethyl-1,3-dioxane-4,6-dione (4.65 g, 32.2 mmol) was added and the reaction heated to reflux for 17.2 hours. The reaction mixture was partitioned between saturated NaHCO₃ and diethyl ether. The aqueous layer was acidified with concentrated HCl, extracted with diethyl ether, washed with brine, dried over MgSO₄, and concentrated in vacuo to give a brown oil (6.94 g) which was used in the next step without further purification.

Step 3. Preparation of methyl [5-(3-chloro-4-fluorophenyl)-4-hydroxy-4-phenyl-2-oxazolinyl]acetate.

A solution of the ester from Step 2 (6.86 g, 19.6 mmol) dissolved in methanol (11 mL) was treated with ammonium acetate (3.17 g, 41.1 mmol), and heated to reflux. After 1.9 hours, the reaction was cooled, additional methanol (65 mL) was added, and the reaction mixture was acidified by adding concentrated sulfuric acid and heated to reflux for an additional 1.4 hours. The reaction mixture was concentrated in vacuo, and the residue was dissolved in ethyl acetate, washed with water, saturated NaHCO₃, and brine, dried over MgSO₄, concentrated in vacuo, and passed through a column of silica gel eluting with 50% ethyl acetate/hexane to give a yellow oil (2.10 g, 29%): ¹H NMR (acetone-d₆) 300 MHz δ 8.30 (br s, 1H) 8.18 (dd, J=7.3 Hz 2.2 Hz, 1H) 8.12 (m, 1H) 7.30-7.50 (m, 6H) 6.60 (d, J= 6.8 Hz, 1H) 3.65 (s, 3H) 3.41 (s, 2H). ¹⁹F NMR (acetone-d₆) 282 MHz -109.78 (m). Mass spectrum: M+Li=370.

Step 4. Preparation of methyl [4-(4-aminosulfonylphenyl)-5-(3-chloro-4-fluorophenyl)]-2-oxazoleacetate

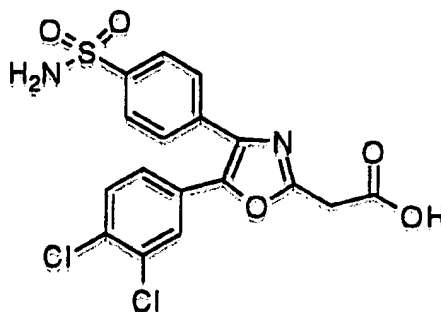
The compound from Step 3 (2.05 g, 5.6 mmol) was stirred with chlorosulfonic acid (10 mL) for 0.33 hours at room temperature and then for 0.25 hours at 75 °C. The reaction was cooled, slowly added to ice water, and extracted with dichloromethane. The dichloromethane layer was stirred with ammonium hydroxide for one hour at room temperature. The organic layer was concentrated in vacuo, dissolved in ethyl acetate, washed with 3N HCl, brine, dried over MgSO₄, concentrated in vacuo and recrystallized from ethyl acetate/hexane to give a white solid (0.58 g, 24%): mp 142-144 °C. ¹H NMR (acetone-d₆) 300 MHz δ 7.92 (d, J=8.5 Hz, 2H) 7.85 (d, J=8.7 Hz, 2H) 7.78 (dd, J=7.1 Hz 2.2 Hz, 1H) 7.62 (m, 1H) 7.44 (t, J=8.8 Hz, 1H) 6.66 (br s, 1H) 4.06 (s, 2H) 3.75 (s, 3H). ¹⁹F NMR (acetone-d₆) 282 MHz -115.94 (m).

High resolution mass spectrum Calc'd. for $C_{18}H_{15}ClFN_2O_5S$:
425.0374. Found: 425.0379.

5 Step 5. Preparation of [4-(4-aminosulfonylphenyl)-5-(3-chloro-4-fluorophenyl)]-2-oxazoleacetic acid

10 The ester from Step 4 (0.55 g, 1.3 mmol) was dissolved in methanol (10 mL), treated with NaOH (0.09 g dissolved in 5 mL water, 2.2 mmol), and stirred at room temperature. After 1 hour, additional NaOH (0.10 g, 2.5 mmol) was added and
15 stirring was continued for 1.4 hours. Water was added and the reaction mixture was extracted with ethyl acetate. The aqueous layer was then acidified with concentrated HCl and extracted with ethyl acetate. The ethyl acetate was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to
20 give a white solid (0.39 g, 74%): mp 222-223 °C. 1H NMR (acetone- d_6) 300 MHz δ 7.92 (d, $J=8.5$ Hz, 2H) 7.85 (d, $J=8.6$ Hz, 2H) 7.79 (dd, $J=7.0$ Hz 2.2 Hz, 1H) 7.62 (m, 1H) 7.44 (t, $J=8.9$ Hz, 1H) 6.67 (br s, 1H) 4.04 (s, 2H). ^{19}F NMR (acetone- d_6) 282 MHz -116.41 (m).

EXAMPLE 40



5 **[4-(4-Aminosulfonylphenyl)-5-(3,4-dichlorophenyl)]-2-**
 oxazoleacetic acid

Step 1. Preparation of 2-hydroxy-2-(3,4-dichlorophenyl)-1-
phenylethanone.

- 10 A solution of 3,4-dichlorobenzaldehyde (25.35 g, 145 mmol) and zinc iodide (0.42 g) in dichloromethane (100 mL) was treated with a solution of trimethylsilylcyanide (20 mL, 150 mmol) in dichloromethane (25 mL). The solution was stirred for 0.33 hours at room temperature, washed with
- 15 saturated NaHCO₃ and brine, dried over MgSO₄, and concentrated in vacuo to give the trimethylsilyl cyanohydrin as an orange oil (36.79 g). The trimethylsilyl cyanohydrin was dissolved in diethyl ether (50 mL) and added dropwise to a solution of phenylmagnesium bromide (144 mmol) in diethyl
- 20 ether (500 mL) while maintaining the temperature between 25-33 °C with an ice water bath. The reaction was allowed to stir for 1.8 hours at room temperature then quenched by adding 3N HCl (160 mL). The organic layer was collected, washed with saturated NaHCO₃ and brine, dried over MgSO₄, and
- 25 concentrated in vacuo to give an orange oil (49.07g). The orange oil was dissolved in 9:1 trifluoroacetic acid/water (100 mL) and stirred for 1.5 hours at room temperature. The reaction was neutralized with solid sodium carbonate, extracted with diethyl ether, washed with brine, dried over

MgSO₄, and concentrated in vacuo to give a yellow solid which was recrystallized from ethyl acetate/iso-octane to give the benzoin (16.35 g, 37%): mp 68-71 °C. ¹H NMR (CDCl₃) 300 MHz δ 7.88 (d, J=7.5 Hz, 2H) 7.57 (m, 1H) 7.44 (m, 3H) 7.37 (d, J=8.3 Hz, 1H) 7.07 (dd, J=8.3 Hz 2.0 Hz, 1H) 5.92 (s, 1H) 4.60 (br s, 1H).

Step 2. Esterification of 2-hydroxy-2-(3,4-dichlorophenyl)-1-phenylethanone

10 The ketone from Step 1 (7.43 g, 26.4 mmol) was dissolved in THF (8 mL), 2,2-dimethyl-1,3 dioxane-4,6-dione (5.92 g, 41.1 mmol) was added and the reaction heated to reflux for 19.9 hours. The reaction mixture was partitioned between saturated NaHCO₃ and diethyl ether. The aqueous layer was
15 acidified with concentrated HCl, extracted with diethyl ether, washed with brine, dried over MgSO₄, and concentrated in vacuo to give a brown oil (6.67 g) which was used in the next step without further purification.

20 Step 3. Preparation of methyl [5-(3,4-dichlorophenyl)-4-hydroxy-4-phenyl-2-oxazolinyl]acetate

The ester from Step 2 (6.67 g, 18.2 mmol) was dissolved in methanol (10 mL), treated with ammonium acetate (2.90 g, 37.6 mmol), and heated to reflux. After 2.0 hours, the
25 reaction was cooled, additional methanol (50 mL) was added, and the reaction mixture was acidified by adding concentrated sulfuric acid and heated to reflux for an additional 0.6 hours. The reaction mixture was concentrated in vacuo, and the residue was dissolved in ethyl acetate, washed with
30 water, saturated NaHCO₃, and brine, dried over MgSO₄, and concentrated in vacuo to give an orange oil (4.38 g) which was used in the next step without further purification.

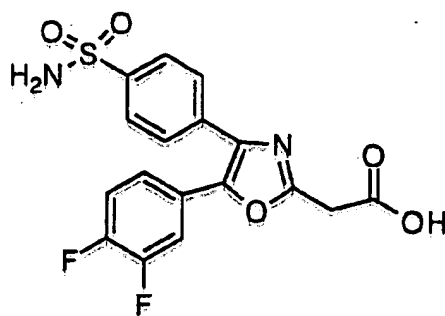
35 Step 4. Preparation of methyl [4-(4-aminosulfonylphenyl)-5-(3,4-dichlorophenyl)-2-oxazoleacetate.

The compound from Step 3 (4.32 g, 11.4 mmol) was stirred with chlorosulfonic acid (13 mL) for 0.4 hours at room temperature and then for 0.6 hours at 75 °C. The reaction was cooled, slowly added to ice water, and extracted with dichloromethane. The dichloromethane was stirred with ammonium hydroxide (20 mL) for 1.1 hours at room temperature. The organic layer was concentrated in vacuo, dissolved in ethyl acetate, washed with 3N HCl, brine, dried over MgSO₄, concentrated in vacuo, passed through a column of silica gel eluting with 50% ethyl acetate/hexane, and recrystallized from ethyl acetate/hexane to give a tan solid (1.20g, 24%): mp 144-153 °C. ¹H NMR (acetone-d₆) 300 MHz 7.94 (d, J=8.5 Hz, 2H) 7.86 (d, J=8.3 Hz, 2H) 7.80 (d, J=1.8 Hz, 1H) 7.67 (d, J=8.3 Hz, 1H) 7.60 (dd, J=8.5 Hz 2.0 Hz, 1H) 6.67 (br s, 1H) 4.07 (s, 2H) 3.75 (s, 3H). High resolution mass spectrum Calc'd. for C₁₈H₁₅Cl₂N₂O₅S: 441.0079. Found: 441.0088.

Step 5. Preparation of [4-(4-aminosulfonylphenyl)-5-(3,4-dichlorophenyl)]-2-oxazoleacetic acid.

The oxazole ester from Step 4 (0.35 g, 0.8 mmol) was dissolved in methanol (10 mL), treated with NaOH (0.07 g dissolved in 5 mL water, 1.8 mmol), and stirred at room temperature. After 1.1 hours, additional NaOH (0.10 g, 2.5 mmol) was added and stirring continued for 1.4 hours. Water was added and the reaction mixture was extracted with ethyl acetate. The aqueous layer was then acidified with concentrated HCl and extracted with ethyl acetate. The ethyl acetate was washed with brine, dried over MgSO₄, and concentrated in vacuo to give a yellow solid (0.33 g, 97%): mp 204-209 °C. ¹H NMR (acetone-d₆) 300 MHz δ 7.94 (d, J=8.9 Hz, 2H) 7.87 (d, J=8.7 Hz, 2H) 7.82 (d, J=2.0 Hz, 1H) 7.67 (d, J=8.3 Hz, 1H) 7.60 (dd, J=8.5 Hz 2.2 Hz, 1H) 6.68 (br s, 1H) 4.05 (s, 2H).

EXAMPLE 41



5 **[4-(4-Aminosulfonylphenyl)-5-(3,4-difluorophenyl)]-2-oxazoleacetic acid**

Step 1. Preparation of 2-hydroxy-2-(3,4-difluorophenyl)-1-phenylethanol.

10 A solution of 3,4-difluorobenzaldehyde (25.33 g, 178 mmol) and zinc iodide (0.13 g) in dichloromethane (100 mL) was treated with a solution of trimethylsilylcyanide (24.5 mL, 184 mmol) in dichloromethane (20 mL). The solution was stirred for 0.25 hours at room temperature, washed with saturated NaHCO₃ and brine, dried over MgSO₄, and

15 concentrated in vacuo to give the trimethylsilyl cyanohydrin as a yellow oil (41.03 g). The trimethylsilyl cyanohydrin was dissolved in diethyl ether (50 mL) and added dropwise to a solution of phenylmagnesium bromide (186 mmol) in diethyl ether (560 mL) while maintaining the temperature between 25-

20 33 °C with an ice water bath. The reaction was stirred for 0.5 hours at room temperature then quenched by adding 3N HCl (150 mL). The organic layer was collected, washed with saturated NaHCO₃ and brine, dried over MgSO₄, and

25 concentrated in vacuo to give an orange oil (49.71g). The orange oil was dissolved in 9:1 trifluoroacetic acid/water (100 mL) and stirred for 0.5 hours at room temperature. The reaction was neutralized with solid sodium carbonate, extracted with ethyl acetate, washed with brine, dried over MgSO₄, and concentrated in vacuo to give a brown solid which

121

was recrystallized from diethyl ether/hexane to give the benzoin (16.35 g, 37%): mp 68-71 °C. ^1H NMR (CDCl_3) 300 MHz δ 7.87 (d, $J=7.1$ Hz, 2H) 7.56 (m, 1H) 7.42 (m, 2H) 7.07 (m, 3H) 5.92 (s, 1H) 4.40 (br s, 1H). ^{19}F NMR (CDCl_3) 282 MHz

5 -136.37 (m) -137.70 (m), Mass spectrum: $M+\text{Li}=255$.

Step 2. Esterification of 2-hydroxy-2-(3,4-difluorophenyl)-1-phenylethanone

10 The ethanone from Step 1 (5.93 g, 23.9 mmol) was dissolved in THF (6 mL), 2,2-dimethyl-1,3-dioxane-4,6-dione (3.70 g, 25.7 mmol) was added and the reaction heated to reflux for 23.7 hours. Additional 2,2-dimethyl-1,3-dioxane-4,6-dione (1.46 g, 10.1 mmol) was added and the reaction was

15 stirred at reflux an additional 19.7 hours. The reaction mixture was partitioned between saturated NaHCO_3 and diethyl ether. The aqueous layer was acidified with concentrated HCl , extracted with diethyl ether, washed with brine, dried over MgSO_4 , and concentrated in vacuo to give a yellow oil

20 (6.05 g) which was used in the next step without further purification.

Step 3. Preparation of methyl [5-(3,4-difluorophenyl)-4-hydroxy-4-phenyl-2-oxazolinyl]acetate

25 The ester from Step 2 (6.03 g, 18.0 mmol) was dissolved in methanol (10 mL), treated with ammonium acetate (3.07 g, 39.8 mmol), and heated to reflux. After 2.4 hours, the reaction was cooled, additional methanol (60 mL) was added, and the reaction mixture was acidified by adding concentrated

30 sulfuric acid and heated to reflux for an additional 1.9 hours. The reaction mixture was concentrated in vacuo, and the residue was dissolved in ethyl acetate, washed with water, saturated NaHCO_3 , and brine, dried over MgSO_4 , and concentrated in vacuo to give an orange oil (4.64 g, 74%)

35 which was used in the next step without further purification.

Step 4. Preparation of methyl-[4-(4-aminosulfonylphenyl)-5-(3,4-difluorophenyl)]-2-oxazoleacetate.

The oxazoline from Step 3 (3.34 g, 9.6 mmol) was stirred
5 with chlorosulfonic acid (13 mL) for 0.4 hours at room
temperature and then for 0.75 hours at 75 °C. The reaction
was cooled, slowly added to ice water, and extracted with
dichloromethane. The dichloromethane was stirred at room
temperature with ammonium hydroxide (20 mL) for 1.1 hours.
10 The organic layer was concentrated in vacuo, dissolved in
ethyl acetate, washed with 3N HCl, brine, dried over MgSO₄,
concentrated in vacuo, passed through a column of silica gel
eluting with 45% ethyl acetate/hexane, and recrystallized
from ethyl acetate/hexane to give a yellow solid (0.71 g,
15 27%): mp 144-149 °C. ¹H NMR (acetone-d₆) 300 MHz δ 7.92 (d,
J=8.7 Hz, 2H) 7.84 (d, J=8.5 Hz, 2H) 7.58 (m, 1H) 7.47 (m,
2H) 6.67 (br s, 1H) 4.06 (s, 2H) 3.75 (s, 3H). ¹⁹F NMR
(acetone-d₆) 282 MHz -138.46 (m) -138.79 (m). High
resolution mass spectrum Calc'd. for C₁₈H₁₅F₂N₂O₅S:
20 409.0670. Found: 409.0686.

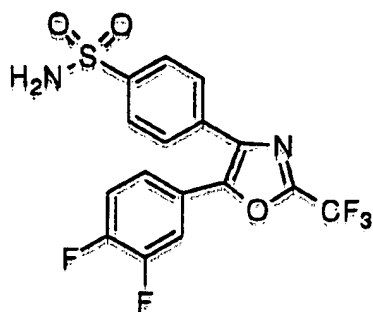
Step 5. Preparation of [4-(4-aminosulfonylphenyl)-5-(3,4-difluorophenyl)]-2-oxazoleacetate.

The oxazole ester from Step 4 (0.64 g, 1.3 mmol) was
25 dissolved in methanol (10 mL), treated with NaOH (0.07 g
dissolved in 5 mL water, 1.8 mmol), and stirred at room
temperature. After one hour, additional NaOH (0.11 g, 2.8
mmol) was added and stirring continued for 1.4 hours. Water
was added and the reaction mixture was extracted with ethyl
30 acetate. The aqueous layer was acidified with concentrated
HCl and extracted with ethyl acetate. The ethyl acetate was
washed with brine, dried over MgSO₄, and concentrated in
vacuo to give a white solid (0.49 g, 80%): mp 223-227 °C. ¹H
NMR (acetone-d₆) 300 MHz δ 7.92 (d, J=8.7 Hz, 2H) 7.85 (d,
35 J=8.7 Hz, 2H) 7.58 (m, 1H) 7.48 (m, 2H) 6.66 (br s, 1H) 4.04

(s, 2H). ^{19}F NMR (acetone- d_6) 282 MHz -138.97 (m) -139.24 (m).

EXAMPLE 42

5



[2-Trifluoromethyl-5-(3,4-difluorophenyl)-4-oxazolyl]benzenesulfonamide

10

Step 1. Preparation of 3-trifluoromethyl-4-phenyl-5-(3,4-difluorophenyl)oxazole.

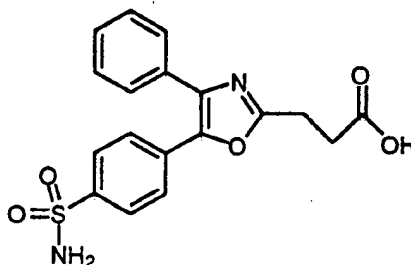
A solution of 2-hydroxy-2-(3,4-difluorophenyl)-1-phenylethanone (Example 41, Step 1) (3.48 g, 14.0 mmol) in dimethylformamide (DMF) (15 mL) was added to a solution of trifluoroacetonitrile (1.85 g, 19.5 mmol) in DMF (150 mL). The reaction was cooled to 5 °C, treated with 1,8-diazabicyclo[5.4.0]undecane (DBU) (2.31 g, 15.2 mmol), and stirred for 15.3 hours at room temperature and 3.5 hours at 90 °C. The reaction mixture was diluted with ethyl acetate, washed with 3N HCl, saturated NaHCO_3 , brine, dried over MgSO_4 , concentrated in vacuo, and passed through a column of silica gel eluting with 10% diethyl ether/hexane to give a clear oil (2.35 g, 52%): ^1H NMR (acetone- d_6) 300 MHz δ 7.66 (m, 3H) 7.47 (m, 5H). ^{19}F NMR (acetone- d_6) 282 MHz -67.02 (s) -137.15 (m) -138.58 (m).

25

Step 2. Preparation of 4-[5-(3,4-difluorophenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide

3-Trifluoromethyl-4-phenyl-5-(3,4-difluorophenyl)oxazole from Step 1 (1.02 g, 3.14 mmol) was stirred with chlorosulfonic acid (9.5 mL) for 0.9 hours at room temperature and then for 2.5 hours at 75 °C. The reaction was cooled, slowly added to ice water, and extracted with dichloromethane. The dichloromethane was stirred with ammonium hydroxide (100 mL) for 14.7 hours at room temperature. The organic layer was concentrated *in vacuo*, dissolved in ethyl acetate, washed with 3N HCl, brine, dried over MgSO₄, concentrated *in vacuo*, and recrystallized from ethyl acetate/hexane to give a tan solid (0.87 g, 69%): mp 146-148 °C. ¹H NMR (acetone-d₆) 300 MHz δ 7.97 (d, J=8.5 Hz, 2H) 7.88 (d, J=8.7 Hz, 2H) 7.71 (m, 1H) 7.58 (m, 2H) 6.70 (br s, 1H). ¹⁹F NMR (acetone-d₆) 282 MHz -67.04 (s) -136.52 (m) -138.30 (m). High resolution mass spectrum Calc'd. for C₁₆H₁₀F₅N₂O₃S: 405.0332. Found: 405.0323.

EXAMPLE 43



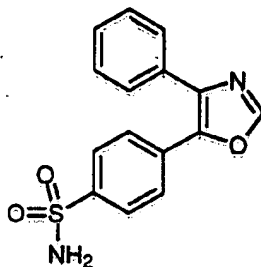
β-[5-(4-Aminosulfonylphenyl)-4-phenyl]-2-oxazolepropionic acid

4,5-Diphenyl-2-oxazolepropionic acid (1.0 g, 3.4 mmol), prepared as in U.S. Patent # 3,578,671, was added to chlorosulfonic acid cooled to 0 °C (25 mL), and the stirred solution was warmed to room temperature for 1.0 hour. The mixture was added dropwise to ice and dichloromethane (50 mL)

125

with stirring. The resultant layers were separated, and the organic layer was washed once with water and added to a 0 °C stirred solution of ammonium hydroxide (10 mL). The mix was stirred for 1.0 hour and extracted with dichloromethane (3 X 50 mL). The combined organic layers were washed with 1 N HCl followed by brine and water, dried over MgSO₄ and concentrated. The crude product was purified by recrystallization from ethyl acetate/hexane to afford a white solid (0.6 g, 47.4%): mp 236-239 °C. ¹H NMR (DMSO-d₆) 300 MHz δ 12.15 (bs, 1H) 7.84 (d, J=8.5 Hz, 2H) 7.68 (d, J=8.5 Hz, 2H) 7.4-7.5 (m, 7H) 3.07 (t, J=7.1 Hz, 2H) 2.78 (t, J=7.1 Hz, 2H). Anal. Calc'd. for C₁₈H₁₆N₂O₅S: C, 58.06; C, 58.22; H, 4.33; H, 4.52; N, 7.52; N, 7.30.

EXAMPLE 44



4-[4-Phenyl-5-oxazolyl]benzenesulfonamide

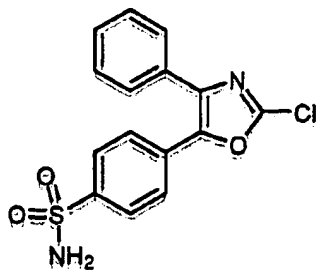
Step 1. Preparation of 4,5-diphenyloxazole.

Benzoin (4.25 g, 20 mmol) was stirred at 0 °C in dichloromethane (150 mL) with triethylamine (2.23 g, 22 mmol). Methanesulfonyl chloride (2.52 g, 22 mmol) was added dropwise. The solution was warmed to room temperature for 1.0 hour. Formamide (10 mL) was added and the mixture was concentrated to remove dichloromethane. The residue was heated to 50 °C overnight, cooled, diluted with ether, washed with 1 N HCl, brine, water dried over MgSO₄, concentrated in vacuo, and passed through a column of silica gel eluting with

(1:16) ethyl acetate/hexane to give a clear oil (3.1 g, 70 %): ^1H NMR (CDCl_3) 300 MHz 7.96 (s, 1H) 7.60-7.70 (m, 4H) 7.31-7.41 (m, 6H). Anal. Calc'd. for $\text{C}_{15}\text{H}_{11}\text{NO}\cdot 1.5 \text{H}_2\text{O}$: C, 80.20; H, 5.10; N, 6.24. Found: C, 80.20; H, 5.07; N, 6.25.

Step 2. Preparation of 4-[4-phenyl-5-oxazolyl]benzenesulfonamide

4,5-Diphenyloxazole from Step 1 (0.5 g, 2.3 mmol) was added to chlorosulfonic acid cooled to 0 °C (5 mL), and the stirred solution was warmed to room temperature for 1.0 hour. The mixture was added dropwise to ice and dichloromethane (50 mL) with stirring. The resultant layers were separated, and the organic layer was washed once with water and added to a 0 °C stirred solution of ammonium hydroxide (10 mL) and stirred for 1.0 hour and extracted with dichloromethane (3 X 50 mL). The combined organic layers were washed with 1 N HCl followed by brine and water, dried over MgSO_4 and concentrated. The residue was purified by recrystallization from ether/hexanes to give a white solid (0.3 g, 44 %): mp 122-125 °C. ^1H NMR (acetone- d_6) 300 MHz δ 8.35 (s, 1H) 7.88 (d, J=8.7 Hz, 2H) 7.79 (d, J=8.7 Hz, 2H) 7.64-7.70 (m, 2H) 7.40-7.5 (m, 3H) 6.68 (bs, 2H). Anal. Calc'd. for $\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}_3\text{S}$: C, 59.99; H, 4.03; N, 9.33. Found: C, 60.09; H, 4.05; N, 9.27.

EXAMPLE 45**5 4-[2-Chloro-4-phenyl-5-oxazolyl]benzenesulfonamide**Step 1. Preparation of 4,5-diphenyloxazolone.

Benzoin (31.8 g, 0.15 mol) and urethane (42.79 g, 0.45 mol) were heated to reflux for 3.0 hours. The hot mixture was poured into water (150 mL). Acetone (150 mL) was added and heat was applied until the mixture dissolved. The solution was cooled and filtered yielding a white solid which was used in the next step without further purification: ¹H NMR (DMSO-d₆) 300 MHz δ 7.2-7.5 (m, 11H).

Step 2. Preparation of 2-chloro-4,5-diphenyl-oxazole.

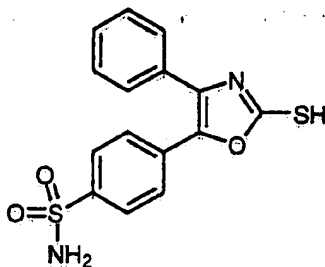
4,5-Diphenyloxazolone from Step 1 (30 g, 0.126 mol), triethylamine (12.8 g, 0.126 mol), and phosphorous oxychloride (96.6 g, 0.63 mol) were stirred at reflux for 4.0 hours. The mixture was concentrated in vacuo and dissolved in ether (250 mL), washed with 1 N HCl, brine, water, dried over MgSO₄ and concentrated to a light yellow oil which was used in the next step without further purification or characterization.

Step 3. Preparation of 4-[2-chloro-4-phenyl-5-oxazolyl]benzenesulfonamide.

2-Chloro-4,5-diphenyl-oxazole from Step 2 (1.53 g, 6 mmol) was added to chlorosulfonic acid cooled to 0 °C (20

mL), and the stirred solution was warmed to room temperature for 1.0 hour. The mixture was added dropwise to ice and dichloromethane (50 mL) with stirring. The resultant layers were separated, and the organic layer was washed once with water and added to a 0 °C stirred solution of ammonium hydroxide (10 mL). The mixture was stirred for 1.0 hour and extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed with 1 N HCl followed by brine and water, dried over MgSO₄ and concentrated. Recrystallization from ethyl acetate/hexanes gave a white solid (1.5 g, 75 %): mp 158-159 °C. ¹H NMR (acetone-d₆) 300 MHz δ 7.98 (d, J=8.7 Hz, 2H) 7.78 (d, J=8.7 Hz, 2H) 7.64-7.70 (m, 2H) 7.42-7.5 (m, 3H) 6.72 (bs, 2H). Anal. Calc'd. for C₁₅H₁₁N₂O₃SCl: C, 53.82; H, 3.31; N, 8.37. Found: C, 53.92; H, 3.32; N, 8.33.

EXAMPLE 46

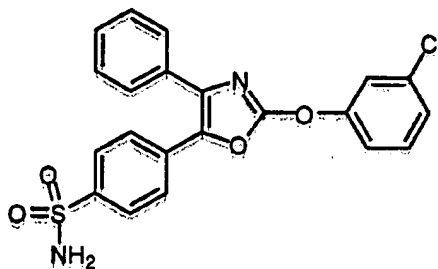


4-[2-Mercapto-4-phenyl-5-oxazolyl]benzenesulfonamide

4-[2-Chloro-4-phenyl-5-oxazolyl]benzenesulfonamide (Example 45) (1.67 g, 5 mmol), dimethylsulfoxide (50 mL), and sodium thiomethoxide (0.70 g, 10 mmol) were stirred at room temperature for 16.0 hours. The mixture was diluted with ethyl acetate (100 mL) washed with 1 N HCl, brine, water, dried over MgSO₄ and concentrated. Recrystallization from ethyl acetate/hexanes gave the product as a brown solid (0.8 g, 48 %): mp 247-249 °C. ¹H NMR (acetone-d₆) 300 MHz δ 12.1 (bs, 1H) 7.89 (d, J=8.7 Hz, 2H) 7.62-7.68 (m, 4H) 7.54-7.59

(m, 3H) 6.7 (bs, 2H). Anal. Calc'd. for $C_{15}H_{12}N_2O_3S_2$: C, 54.20; H, 3.64; N, 8.43. Found: C, 54.27; H, 3.68; N, 8.41.

EXAMPLE 47

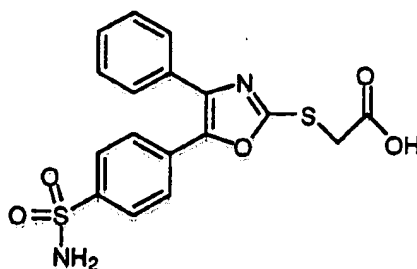


4-[2-(3-Chlorophenoxy)-4-phenyl-5-oxazolyl]benzenesulfonamide

4-[2-Chloro-4-phenyl-5-oxazolyl]benzenesulfonamide (Example 45) (1.67 g, 5 mmol), DMF (20 mL), potassium carbonate (1.38 g, 10 mmol), and 3-chlorophenol (0.64 g, 5 mmol) were stirred at room temperature for 16.0 hours, diluted with ethyl acetate (100 mL), washed with 1 N HCl, brine and water, dried over $MgSO_4$ and concentrated. The residue was dissolved in ethyl acetate/hexanes (1:1) and filtered through silica. The eluant was concentrated and the residue recrystallized from ethyl acetate/hexanes to afford the product as a light yellow solid (1.4 g, 66 %): mp 138-140 °C. 1H NMR (acetone- d_6) 300 MHz δ 7.92 (d, $J=8.9$ Hz, 2H) 7.75 (d, $J=8.9$ Hz, 2H) 7.7 (m, 1H) 7.60-7.65 (m, 2H) 7.54-7.56 (m, 2H) 7.38-7.46 (m, 4H) 6.90 (bs, 2H). Anal. Calc'd. for $C_{21}H_{15}N_2O_4SCl$: C, 59.09; H, 3.54; N, 6.56. Found: C, 59.02; H, 3.55; N, 6.61.

EXAMPLE 48

130

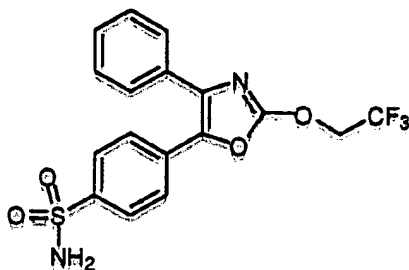


5-(4-Aminosulfonylphenyl)-4-phenyl-2-oxazolemercaptoacetic acid

5

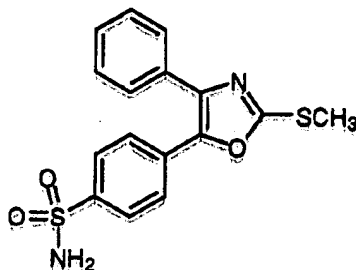
4-[2-Chloro-4-phenyl-5-oxazolyl]benzenesulfonamide (Example 45) (1.67 g, 5 mmol), DMF (20 mL), sodium hydride (1.32 g, 5.5 mmol), and mercaptoacetic acid, sodium salt (0.63 g, 5.5 mmol) were stirred at room temperature for 16.0 hours. The solution was diluted with ethyl acetate (100 mL), washed with 1 N HCl, brine and water, dried over MgSO_4 and concentrated. The residue was purified by flash column chromatography eluting with ethyl acetate:methanol:water (20:10:1) to provide the product as a light yellow solid (0.8 g, 41 %): mp 235-238 °C. ^1H NMR (D_2O) 300 MHz δ 7.62 (d, J=8.7 Hz, 2H) 7.43 (d, J=8.7 Hz, 2H) 7.32 (m, 5H) 3.76 (s, 2H). High resolution mass spectrum Calc'd. for $\text{C}_{17}\text{H}_{15}\text{N}_2\text{O}_5\text{S}_2$: 391.0422. Found: 391.0423.

EXAMPLE 49



5 4-[4-Phenyl-2-(2,2,2-trifluoroethoxy)-5-oxazolyl]benzenesulfonamide

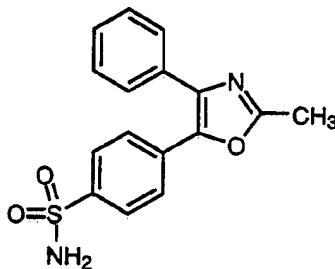
4-[2-Chloro-4-phenyl-5-oxazolyl]benzenesulfonamide
(Example 45) (1.67 g, 5 mmol), DMF (20 mL), potassium
10 carbonate (3.38 g, 10 mmol), and 2,2,2-trifluoroethanol (0.75 g, 7.5 mmol) were stirred at room temperature for 16.0 hours. The solution was diluted with ethyl acetate (100 mL), washed with 1 N HCl, brine and water, dried over MgSO₄ and concentrated. The residue was dissolved in ethyl
15 acetate/hexanes (1:1) and filtered through silica. The eluant was concentrated and recrystallized from ethyl acetate/hexanes to provide the product was a white solid (1.4 g, 70 %): mp 180-182 °C. ¹H NMR (CDCl₃) 300 MHz δ 7.85 (d, J=8.5 Hz, 2H) 7.65 (d, J=8.5 Hz, 2H) 7.6 (m, 2H) 7.4 (m, 3H)
20 4.9 (dd, J=8.1 Hz, 2H) 4.85 (bs, 2H). Anal. Calc'd. for C₁₇H₁₃N₂O₄S₁F₃: C, 51.26; H, 3.29; N, 7.03. Found: C, 51.32; H, 3.30; N, 7.01.

EXAMPLE 50

5 **4-[2-(Methylthio)-4-phenyl-5-oxazolyl]benzenesulfonamide**

4-[2-Chloro-4-phenyl-5-oxazolyl]benzenesulfonamide (Example 45) (1.67 g, 5 mmol), methanol (50 mL), and sodium
10 thiomethoxide (0.39 g, 5.5 mmol) were stirred at room temperature for 16.0 hours. The solution was concentrated and dissolved in ethyl acetate (100 mL), washed with 1 N HCl, brine and water, dried over MgSO₄ and concentrated. The
15 residue was recrystallized from ethyl acetate/hexanes to give the product was a light yellow solid (1.4 g, 81 %): mp 162-164 °C. ¹H NMR (CDCl₃) 300 MHz δ 7.85 (d, J=8.9 Hz, 2H) 7.68 (d, J=8.9 Hz, 2H) 7.6 (m, 2H) 7.4 (m, 3H) 4.85 (bs, 2H) 2.75 (s, 3H). Anal. Calc'd. for C₁₆H₁₄N₂O₃S₂: C, 55.48; H, 4.07; N, 8.09. Found: C, 55.56; H, 4.10; N, 8.15.

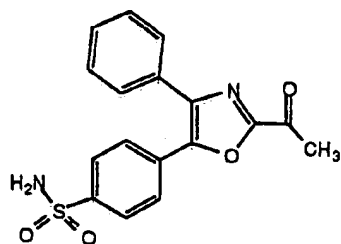
20

EXAMPLE 51

25 **4-[2-Methyl-4-phenyl-5-oxazolyl]benzenesulfonamide**

Chlorosulfonic acid (25 mL) was cooled to -78 °C with stirring and 2-methyl-4,5-diphenyloxazole (Aldrich) (2.0 g, 8.5 mmol) was added, and the stirred solution was warmed to room temperature for 4.0 hours. The mixture was then added dropwise to ice and dichloromethane (100 mL) with stirring. The resultant layers were separated, and the organic layer was washed once with water and added to a 0 °C stirred solution of ammonium hydroxide (20 mL). The solution was stirred for 1.0 hour and extracted with dichloromethane (3 X 50 mL). The combined organic layers were washed with 1 N HCl followed by brine and water, dried over MgSO₄ and concentrated. The residue was purified by recrystallization from ethanol/water to give the product as a white solid (1.6 g, 60 %): mp 176-178 °C. ¹H NMR (acetone-d₆) 300 MHz δ 7.92 (d, J=8.7 Hz, 2H) 7.74 (d, J=8.7 Hz, 2H) 7.61-7.66 (m, 2H) 7.40-7.48 (m, 3H) 6.68 (bs, 2H) 2.53 (s, 3H). Anal. Calc'd. for C₁₆H₁₄N₂O₃S: C, 61.13; H, 4.49; N, 8.91. Found: C, 60.89; H, 4.53; N, 8.85.

Example 52



2-[5-[(4-Aminosulfonyl)phenyl]-4-phenyloxazol-2-yl]ethan-2-one

Step 1: Preparation of 2-[5-[(4-aminosulfonyl)phenyl]-4-phenyloxazol-2-yl]- (2-hydroxy)ethane

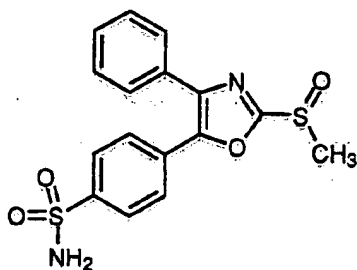
A solution of 2-bromo-2-[(4-aminosulfonyl)phenyl]-1-phenylethanone (0.5 g, 1.41 mmol) in 3 mL of anhydrous DMF was added to a suspension of lactic acid sodium salt (0.16 g, 1.41 mmol) in 2 mL of anhydrous DMF, and the reaction mixture was stirred for 18 h at room temperature. The DMF was then removed under vacuum. Ethyl acetate (50 mL) was added to the concentrated residue, and the mixture was filtered. The filtrate was concentrated and dried under vacuum. Acetic acid (5 mL) and ammonium acetate (0.33 g, 4.28 mmol) were added to this concentrated residue. This reaction mixture was heated at 100 °C for 3 h, cooled to room temperature, and water (100 mL) was added to the cooled reaction mixture. The aqueous solution was extracted with ethyl acetate (1 x 150 mL). The organic phase was separated and washed with water (2 x 100 mL), saturated sodium bicarbonate (2 x 100 mL), brine (2 x 100 mL) and dried over magnesium sulfate, filtered and concentrated. The concentrated residue was purified by flash chromatography on silica gel eluting with 45% ethyl acetate in hexane to give 0.26 g (57%) of 2-[5-[(4-aminosulfonyl)-phenyl]-4-phenyl-oxazol-2-yl]- (2-hydroxy)ethane as a yellow solid. ¹H NMR (CDCl₃/300 MHz) 1.72 (d, 3H, J = 6.60 Hz), 2.69 (d, 1H, J = 5.50 Hz), 4.87 (bs, 2H), 5.05-5.13 (m, 1H), 7.41-7.43 (m, 3H), 7.56-7.60 (m, 2H), 7.72 (d, 2H, J = 8.40 Hz), 7.89 (d, 2H, J = 8.70 Hz). HRMS (calcd for C₁₇H₁₆N₂O₄S₁ 345.0909) 345.0896.

Step 2: Preparation of 2-[5-[(4-aminosulfonyl)phenyl]-4-phenyloxazol-2-yl]ethan-2-one

The 2-[5-[(4-aminosulfonyl)phenyl]-4-phenyloxazol-2-yl](2-hydroxy)ethane (0.3 g, 0.87 mmol) from Step 1 was suspended in 15 mL of methylene chloride. Pyridinium

135

chlorochromate (0.3 g, 1.4 mmol) and molecular sieves (0.4 g) were added, and the resulting mixture was stirred for 10 minutes at room temperature. Acetone (5 mL) was added, and the reaction mixture was stirred for 48 h at room temperature. The reaction mixture was filtered, and the filtrate was concentrated. The concentrated residue was crystalized from ethyl acetate and hexane to give 0.11 g (30%) of 2-[5-[(4-aminosulfonyl)phenyl]-4-phenyloxazol-2-yl]ethan-2-one as a white solid, m.p. 208.5-210.2 °C. ¹H NMR(DMSO-d₆/300 MHz) 2.65 (s, 3H), 7.45-7.52 (m, 5H), 7.59-7.62 (m, 2H), 7.78 (d, 2H, J = 8.40 Hz), 7.90 (d, 2H, J = 8.40 Hz). HRMS (calcd. for C₁₇H₁₄N₂O₄S₁ 343.0753) 343.0728.

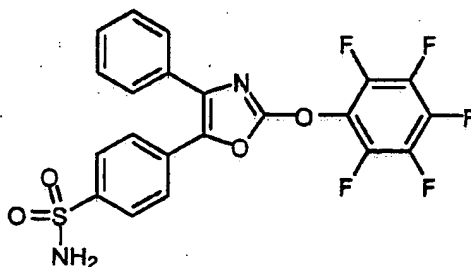
EXAMPLE 53**4-[2-Methylsulfinyl)-4-phenyl-5-oxazolyl]benzenesulfonamide**

20

4-[2-Methylthio-4-phenyl-5-oxazolyl]benzenesulfonamide (Example 50) (0.5 g, 1.44 mmol), ethanol (100 mL), water (50 mL), and Oxone[®] (potassium peroxymonosulfate, 0.88 g, 1.44 mmol) were stirred at room temperature for 16.0 hours. Sodium metabisulfite (5 g) and water (50 mL) were added and the resulting mixture stirred for 0.25 hours before the addition of ethyl acetate (200 mL). The organic layer was separated and washed with brine and water, dried over MgSO₄ and concentrated. The residue was purified by flash chromatography eluting with ethyl acetate:hexanes (1:3). The

- first material collected was concentrated and recrystallized to yield 4-[2-methylsulfonyl]-4-phenyl-5-oxazolyl]benzenesulfonamide as a white solid (0.3 g, 55 %): mp 186-188 °C. ¹H NMR (DMSO-d₆) 300 MHz δ 7.92 (d, J=8.5 Hz, 2H) 7.81 (d, J=8.5 Hz, 2H) 7.6 (m, 2H) 7.48 (m, 5H) 3.3 (s, 3H). Anal. Calc'd. for C₁₆H₁₄N₂O₅S₂: C, 50.78; H, 3.73; N, 7.40. Found: C, 50.79; H, 3.72; N, 7.38. The second material collected was concentrated and recrystallized to yield 4-[2-methylsulfinyl]-4-phenyl-5-oxazolyl]benzenesulfonamide as a white solid (0.16 g, 31 %): mp 174-176 °C. ¹H NMR (DMSO-d₆) 300 MHz δ 7.9 (d, J=8.5 Hz, 2H) 7.8 (d, J=8.5 Hz, 2H) 7.6 (m, 2H) 7.48 (m, 5H) 3.2 (s, 3H). Anal. Calc'd. for C₁₆H₁₄N₂O₄S₂: C, 53.03; H, 3.89; N, 7.73. Found: C, 53.08; H, 3.85; N, 7.66.

EXAMPLE 54

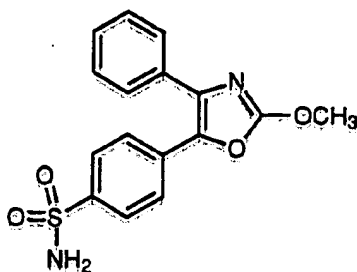


- 4-[2-(2,3,4,5,6-Pentafluorophenoxy)-4-phenyl-5-oxazolyl]benzenesulfonamide

- 4-[2-Chloro-4-phenyl-5-oxazolyl]benzenesulfonamide (Example 45) (1.0 g, 3 mmol), DMF (20 mL), potassium carbonate (0.83 g, 6 mmol), and pentafluorophenol (0.55 g, 3 mmol) were stirred at room temperature for 16.0 hours. The solution was diluted with ethyl acetate (100 mL), washed with 1 N HCl, brine and water, dried over MgSO₄ and concentrated. The residue was dissolved in ethyl acetate/hexanes (1:1) and filtered through silica and the eluant concentrated and

recrystallized from ethyl acetate/hexanes to afford the product was a white solid (0.4 g, 28 %): mp 146-148 °C. ^1H NMR (DMSO- d_6) 300 MHz δ 7.88 (d, $J=8.5$ Hz, 2H) 7.71 (d, $J=8.5$ Hz, 2H) 7.56 (m, 2H) 7.42-7.48 (m, 5H).

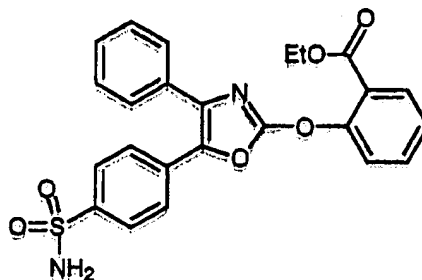
5

EXAMPLE 55

10 4-[2-Methoxy-4-phenyl-5-oxazolyl]benzenesulfonamide

4-[2-Chloro-4-phenyl-5-oxazolyl]benzenesulfonamide (Example 45) (1.0 g, 3 mmol), methanol (15 mL), and sodium methoxide (25 % in methanol) (0.65 g, 6 mmol) were stirred at room temperature for 16.0 hours. Water was added until crystals appeared that were isolated by filtration to afford the desired product as a white solid (0.6 g, 61 %): mp 180-182 °C. ^1H NMR (DMSO- d_6) 300 MHz δ 7.81 (d, $J=8.5$ Hz, 2H) 7.62 (d, $J=8.5$ Hz, 2H) 7.57 (m, 2H) 7.38-7.46 (m, 5H) 4.12 (s, 3H). Anal. Calc'd. for $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_4\text{S}$: C, 58.17; H, 4.27; N, 8.48. Found: C, 58.12; H, 4.31; N, 8.44.

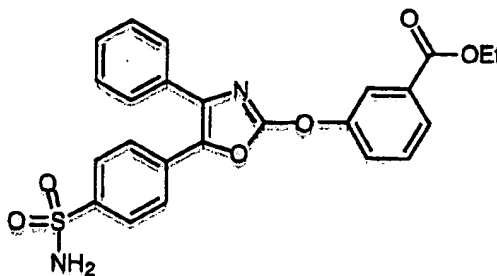
EXAMPLE 56



5 **Ethyl 2-[[5-(4-aminosulfonylphenyl)-4-phenyl-2-oxazolyl]oxy]benzoate**

4-[2-Chloro-4-phenyl-5-oxazolyl]benzenesulfonamide (Example 45) (1.0 g, 3 mmol), DMF (20 mL), potassium carbonate (0.46 g, 3.3 mmol), and ethyl salicylate (0.55 g, 3.3 mmol) were stirred at room temperature for 16.0 hours, diluted with ethyl acetate (100 mL), washed with 1 N HCl, brine and water, dried over MgSO_4 and concentrated. The residue was dissolved in ethyl acetate/hexanes (1:1) and filtered through silica. The eluant was concentrated and recrystallized from ethyl acetate/hexanes to give the product was a white solid (0.7 g, 50 %): mp 183-184 °C. ^1H NMR ($\text{CDCl}_3/\text{CD}_3\text{OD}$) 300 MHz 8.12 (dd, $J=1.8$ Hz and $J=7.8$ Hz, 1H) 7.86 (d, $J=8.5$ Hz, 2H) 7.62-7.72 (m, 3H) 7.38-7.54 (m, 7H) 4.35 (dd, $J=7.2$ Hz, 2H) 1.3 (t, $J=7.2$ Hz, 3H). Anal. Calc'd. for $\text{C}_{24}\text{H}_{20}\text{N}_2\text{O}_6\text{S}$: C, 62.06; H, 4.34; N, 6.03. Found: C, 61.85; H, 4.37; N, 5.91.

EXAMPLE 57

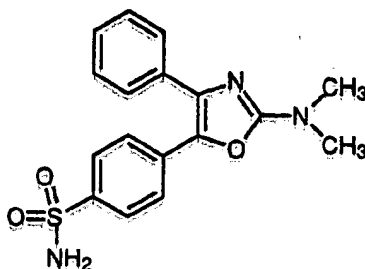


5 **Ethyl 3-[[5-(4-aminosulfonylphenyl)-4-phenyl-2-oxazolyl]oxy]benzoate**

4-[2-Chloro-4-phenyl-5-oxazolyl]benzenesulfonamide (Example 45) (1.0 g, 3 mmol), DMF (20 mL), potassium carbonate (0.46 g, 3.3 mmol), and ethyl 3-hydroxybenzoate (0.55 g, 3.3 mmol) were stirred at room temperature for 16.0 hours. The solution was diluted with ethyl acetate (100 mL), washed with 1 N HCl, brine and water, dried over MgSO₄ and concentrated. The residue was dissolved in ethyl acetate/hexanes (1:1), filtered through silica and the eluant was concentrated and recrystallized from ethyl acetate/hexanes to give the product as a white solid (0.6 g, 43 %): mp 157-158 °C. ¹H NMR (CDCl₃/CF₃CO₂H) 300 MHz δ 8.12 (dd, J=1.6 Hz and J=0.6 Hz, 1H) 7.94-8.0 (dt, J=1.0 Hz and J=7.8 Hz, 1H) 7.89 (d, J=8.7 Hz, 2H) 7.72 (d, J=8.7 Hz, 2H) 7.67 (m, 1H) 7.60 (m, 2H) 7.52 (m, 1H) 7.4 (m, 3H) 4.56 (s, 2H) 4.4 (q, J=7.1 Hz, 2H) 1.4 (t, J=7.1 Hz, 3H). Anal. Calc'd. for C₂₄H₂₀N₂O₆S: C, 62.06; H, 4.34; N, 6.03. Found: C, 62.00; H, 4.36; N, 5.95.

25

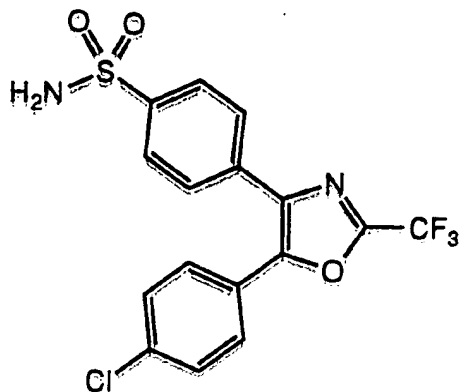
EXAMPLE 58



5 4-[2-(N,N-Dimethylamino)-4-phenyl-5-oxazolyl]benzenesulfonamide

 2-Chloro-4-phenyl-5-oxazolyl]benzenesulfonamide
(Example 45) (1.0 g, 3 mmol) and 40 % aqueous dimethylamine
10 (25 mL) were stirred at room temperature for 16.0 hours,
diluted with ethyl acetate (100 mL), washed with brine and
water, dried over MgSO₄ and concentrated. The residue was
recrystallized from ethyl acetate/hexanes to afford the
product as a light yellow/green solid (0.6 g, 58 %): mp 254-
15 256°C. ¹H NMR (DMSO-d₆) 300 MHz 7.74 (d, J=8.7 Hz, 2H) 7.56
(m, 4H) 7.38-7.46 (m, 3H) 7.33 (bs, 2H) 3.08 (s, 6H). Anal.
Calc'd. for C₁₇H₁₇N₃O₃S: C, 57.31; H, 5.21; N, 11.79.
Found: C, 57.32; H, 5.23; N, 11.73.

EXAMPLE 59



5 4-[5-(4-Chlorophenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide

Step 1. Preparation of 2-hydroxy-2-(4-chlorophenyl)-1-phenylethanone.

- 10 A solution of 4-chlorobenzaldehyde (9.86 g, 70 mmol) and zinc iodide (0.18 g) in dichloromethane (40 mL) was treated with a solution of trimethylsilyl cyanide (9 mL, 71 mmol) in dichloromethane (20 mL). The solution was stirred for 0.33 hours at room temperature, washed with water and saturated
- 15 NaHCO₃, dried over MgSO₄, and concentrated in vacuo to give the trimethylsilyl cyanohydrin as an orange oil (13.90 g). The trimethylsilyl cyanohydrin was dissolved in diethyl ether (50 mL) and added dropwise to a solution of phenylmagnesium bromide (69 mmol) in diethyl ether (269 mL) while maintaining
- 20 the temperature between 15-28 °C with an ice water bath. The reaction was stirred for 0.75 hours at room temperature then quenched by adding 3N HCl (50 mL). The organic layer was collected, washed with saturated NaHCO₃ and brine, dried over MgSO₄, and concentrated in vacuo to give a yellow solid
- 25 (13.06 g). The yellow solid was dissolved in 9:1 trifluoroacetic acid/water (30 mL) and stirred for 1.6 hours

at room temperature. The reaction was neutralized with solid sodium carbonate, extracted with ethyl acetate, washed with 10% Na_2CO_3 and brine, dried over MgSO_4 , concentrated in vacuo to give a yellow solid (9.43 g) and used in the next step without further purification.

Step 2. Preparation of 2-trifluoromethyl-4-phenyl-5-(4-chlorophenyl)oxazole.

Trifluoroacetonitrile (1.5 g, 15.8 mmol) was bubbled into DMF (100 mL). This solution was cooled to 0 °C and 4'-chlorobenzoin (Example 37, Step 1) (2.5 g, 10 mmol) was added. DBU (1.83 g, 12 mmol) was added and the solution was warmed to room temperature for 4 hours. The reaction was heated to approximately 100 °C for an additional 4 hours. The solution was cooled to room temperature, poured into 400 mL 1N HCl and extracted with 500 mL ethyl acetate. The organics were washed consecutively with 1N HCl (400 mL), NaHCO_3 (saturated) (400 mL) and brine (400 mL), dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography eluting with 10% ether in hexane to give a white solid (2.2 g, 67%): mp 53-53 °C. Anal. Calc'd. for $\text{C}_{16}\text{H}_9\text{NOClF}_3$: C, 59.37; H, 2.80; N, 4.33. Found: C, 59.35; H, 2.76; N, 4.25.

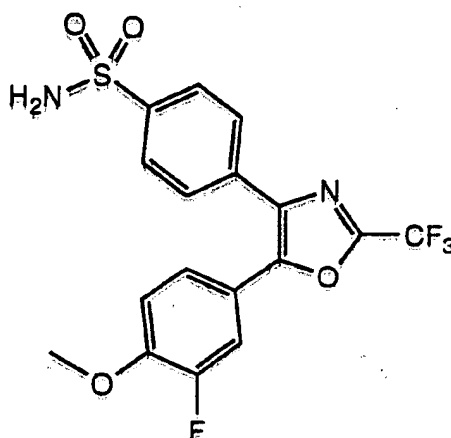
Step 3. Preparation of 4-[2-trifluoromethyl-5-(4-chlorophenyl)-4-oxazolyll]benzenesulfonamide.

2-Trifluoromethyl-4-phenyl-5-(4-chlorophenyl)oxazole (Step 2) (0.9 g, 2.8 mmol) was added to chlorosulfonic acid, cooled to 0 °C (25 mL), and the reaction was warmed to room temperature for 5 hours. The solution was carefully poured into ice water and extracted with three 75 mL portions of dichloromethane. The combined organics were washed once with brine (75 mL) and stirred over ice cold NH_4OH (125 mL) for 2 hours. The dichloromethane layer was separated, washed consecutively with 1N HCl (2 x 75 mL), NaHCO_3 (saturated) (75

mL) and brine (75 mL), dried over Na_2SO_4 and concentrated. The crude material was crystallized from ethyl acetate/hexane to yield 4-[5-(4-chlorophenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide (0.84 g, 75%): mp 167-168 °C.

5 Anal. Calc'd. for $\text{C}_{16}\text{H}_{10}\text{N}_2\text{O}_3\text{SClF}_3$: C, 47.71; H, 2.50; N, 6.96. Found: C, 47.62; H, 2.44; N, 6.88.

EXAMPLE 60



4-[5-(3-Fluoro-4-methoxyphenyl)-2-trifluoromethyl)-4-oxazolyl]benzenesulfonamide

15 Step 1. Preparation of 3-fluoro-p-anisaldehyde silyl cyanohydrin.

3-Fluoro-p-anisaldehyde (14.68 g, 95.2 mmol) was dissolved in anhydrous methylene chloride (300 mL) and ZnI_2 (0.4 g) was added. Trimethylsilyl cyanide (12.7 g, 95.2 mmol) and methylene chloride (75 mL) were added dropwise over 20 minutes. The reaction was stirred an additional 20 minutes and separated. The organics were washed consecutively with water (350 mL), NaHCO_3 (saturated) (300 mL) and brine (300 mL). The methylene chloride was dried 25 over Na_2SO_4 and concentrated to yield silyl cyanohydrin (24.52 g, 100%) which was used without further purification.

Step 2. Preparation of 3'-fluoro-4'-methoxy benzoin.

- 3-Fluoro-p-anisaldehyde silyl cyanohydrin (from Step 1) (24.52 g, 96.8 mmol) and diethyl ether (75 mL) added dropwise to the solution of diethyl ether (250 mL) and phenyl magnesium bromide (3M in ether, 34 mL) were added at such a rate that the reaction temperature did not rise above 30 °C. Upon complete addition, the reaction (which now contained a gummy precipitate) was stirred an additional 15 minutes at which time 1N HCl (400 mL) was added and the reaction stirred until all solids were dissolved. The reaction was poured into a 1L separatory funnel and the layers separated. The organics were washed with NaHCO₃ (saturated) (400 mL) and brine (400 mL), dried over Na₂SO₄ and concentrated to yield a mixture of benzoin and silyl benzoin. The crude product was dissolved in 90% TFA (75 mL) and stirred for 15 minutes. The TFA solution was poured into saturated NaHCO₃ (aq.). The benzoin was extracted with ethyl acetate (350 mL) and washed with NaHCO₃ (saturated) (300 mL) and brine (300 mL). Crystallization of crude benzoin from ether and hexane yielded a first crop of crystals which were >99% pure (14.9 g): mp 84-85 °C. Anal. Calc'd. for C₁₅H₁₃O₃F: C, 69.22; H, 5.03. Found: C, 69.13; H, 5.07.

Step 3. Preparation of 2-trifluoromethyl-4-phenyl-5-(3'-fluoro-4'-methoxyphenyl)oxazole.

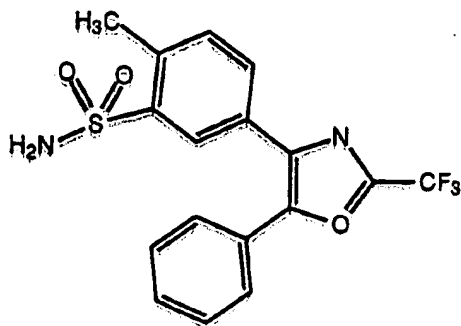
- Trifluoroacetonitrile 0.92 g (9.7 mmol) was added to a solution of DMF (100 ml). This solution was cooled to 0 °C and 3'-fluoro-4'-methoxy benzoin from Step 2 (2.08 g, 8 mmol) was added. DBU (1.45 g, 9.7 mmol) was added and the solution was warmed to room temperature for 4 hours. The reaction was heated to approximately 100 °C for an additional 4 hours. The solution was cooled to room temperature, poured into 400 mL 1N HCl and extracted with 500 mL ethyl acetate. The organics were washed consecutively with 1N HCl (400 mL),

NaHCO₃ (saturated) (400 mL) and brine (400 mL) dried over Na₂SO₄ and concentrated. The crystalline solid residue was recrystallized from ether and hexane to yield analytically pure oxazole (2.32 g, 86%); mp 75-76 °C. Anal. Calc'd. for C₁₇H₁₁NO₂F₄: C, 60.54; H, 3.29; N, 4.15. Found: C, 60.62; H, 3.30; N, 4.18.

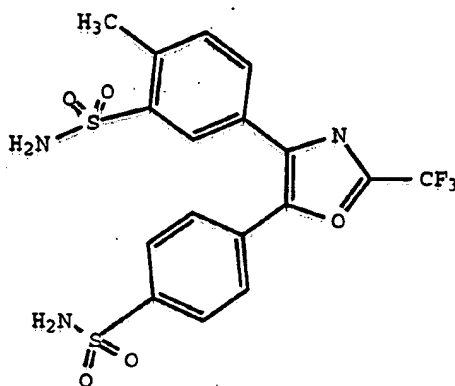
Step 4. Preparation of 4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide

2-Trifluoromethyl-4-phenyl-5-(3-fluoro-4-methoxyphenyl)oxazole from Step 3 (337 mg, 1 mmol) was added to chlorosulfonic acid cooled to 0 °C (10 mL) and the reaction was warmed to room temperature for 3 hours. The solution was carefully poured into ice water and extracted with three 75 mL portions of dichloromethane. The combined organics were washed once with brine (75 mL) and stirred over ice cold NH₄OH (125 mL) for 2 hours. The dichloromethane layer was separated and washed consecutively with 1N HCl (2 x 75 mL), NaHCO₃ (saturated) (75 mL) and brine (75 mL), dried over Na₂SO₄ and concentrated. The crude material was chromatographed over SiO₂ eluting with a gradient from 10% - 35% ethyl acetate in hexane to yield 4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide (20 mg, 5%); mp 150-151 °C. ¹H NMR (acetone-d₆), 300 MHz δ 3.99 (s, 3H), 6.69 (s, 2H), 7.32 (t, 1H), 7.51 (m, 2H), 7.85 (d, J=8.3 Hz, 2H), 7.97 (d, J=8.3 Hz, 2H).

146

EXAMPLE 61

5 **4-Methyl-3-[5-phenyl-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide**

EXAMPLE 62

10

4-[4-(3-Aminosulfonyl-4-methylphenyl)-2-trifluoromethyl-5-oxazolyl]benzenesulfonamide

15 Step 1. Preparation of 2-hydroxy-2-phenyl-1-(4-methylphenyl)ethanone.

The trimethylsilyl cyanohydrin of benzaldehyde Example 34, Step 1 (5.0 g, 24.4 mmol) was dissolved in diethyl ether (50 mL) and added dropwise to a solution of 4-methylphenylmagnesium bromide (29.3 mmol) in diethyl ether

20

(130 mL) while maintaining the temperature between 23-35 °C with an ice water bath. The reaction was stirred for 0.5 hours at room temperature. At this time 1N HCl (100 mL) and ether (150 mL) were added and the layers separated. The organic layer was washed with saturated NaHCO₃ and brine, dried over Na₂SO₄, and concentrated in vacuo to give a yellow oil. The yellow oil was dissolved in 9:1 trifluoroacetic acid/water (30 mL) and stirred for 0.5 hours at room temperature. The reaction was neutralized with solid sodium bicarbonate, extracted with ethyl acetate, washed with saturated NaHCO₃ and brine, dried over Na₂SO₄, concentrated in vacuo and recrystallized from diethyl ether/hexane to give the benzoin (2.54 g, 46%): ¹H NMR (CDCl₃) 300 MHz, δ 2.35 (s, 3H), 4.45 (broad s, 1H), 5.92 (s, 1H), 7.19 (m, 2H), 7.32 (m, 3H), 7.82 (m, 2H).

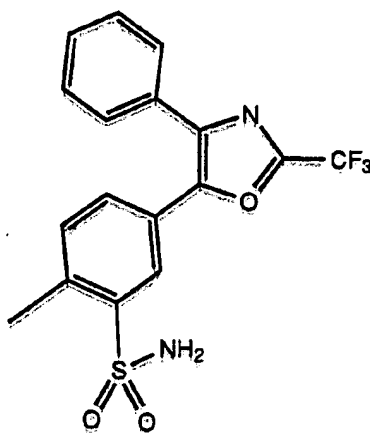
Step 2. Preparation of 2-trifluoromethyl-4-(4-methylphenyl)-5-phenyloxazole.

Trifluoroacetonitrile (0.84 g, 8.84 mmol) was added to DMF (100 mL). This solution was cooled to 0 °C and 4-methylbenzoin from Step 1 (1.36 g, 6 mmol) was added. DBU (1.35 g, 8.84 mmol) was added and the solution was warmed to room temperature for 4 hours. The reaction was then heated to approximately 100 °C for an additional 4 hours. The solution was cooled to room temperature, poured into 400 mL 1N HCl and extracted with 500 mL ethyl acetate. The organics were washed consecutively with 1N HCl (400 mL), NaHCO₃ (saturated) (400 mL) and brine (400 mL), dried over Na₂SO₄ and concentrated. The residue was purified by silica gel chromatography eluting with 1% ether in hexane to give a white solid (0.72 g, 40%): mp 49-50 °C. Anal. Calc'd. for C₁₇H₁₂NOF₃: C, 67.33; H, 3.99; N, 4.62. Found: C, 67.27; H, 3.99; N, 4.58.

Step 3. Preparation of 2-trifluoromethyl-4-(4-methylphenyl)-5-phenyloxazole.

- 2-Trifluoromethyl-4-(4-methylphenyl)-5-phenyloxazole from Step 2 (0.4 g) was added to chlorosulfonic acid (10 mL) cooled to 0 °C and the reaction was warmed to room temperature for 2 hours. The solution was carefully poured into ice water and extracted with three 75 mL portions of dichloromethane. The combined organics were washed once with brine (75 mL) and stirred over ice cold NH_4OH (125 mL) for 2 hours. The dichloromethane layer was separated and washed consecutively with 1N HCl (2 x 75 mL), NaHCO_3 (saturated) (75 mL) and brine (75 mL), dried over Na_2SO_4 and concentrated. The crude material was chromatographed, eluting with a gradient from 10-60% ethyl acetate in hexane to yield 4-methyl-3-[5-phenyl-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide (141 mg, 28%): mp 150-151 °C; Anal. Calc'd. for $\text{C}_{17}\text{H}_{13}\text{N}_2\text{O}_3\text{SF}_3$: C, 53.40; H, 3.43; N, 7.27. Found: C, 53.33; H, 3.48; N, 7.27; and 4-[4-(3-aminosulfonyl-4-methylphenyl)-2-trifluoromethyl-5-oxazolyl]benzenesulfonamide (150 mg, 25%): mp 241-242 °C; Anal. Calc'd. for $\text{C}_{17}\text{H}_{14}\text{N}_3\text{O}_5\text{S}_2\text{F}_3$: C, 44.25; H, 3.06; N, 9.11; Found: C, 44.34; H, 3.07; N, 9.05.]

EXAMPLE 63



5 **4-Methyl-3-[4-phenyl-2-trifluoromethyl-5-oxazolyl]benzenesulfonamide**

Step 1. Preparation of 2-hydroxy-2-(4-methylphenyl)-1-phenylethanone.

- 10 A solution of p-tolulaldehyde (33.55 g, 279 mmol) and trimethylsilyl cyanide (38 mL, 285 mmol) in dichloromethane (160 mL) was treated with zinc iodide (0.34 g). The solution was stirred for 0.33 hours at room temperature, washed with water and saturated NaHCO₃, dried over MgSO₄, and
- 15 concentrated in vacuo to give the trimethylsilyl cyanohydrin as a yellow oil (59.76 g). The trimethylsilyl cyanohydrin was dissolved in diethyl ether (200 mL) and added dropwise to a solution of phenylmagnesium bromide (285 mmol) in diethyl ether (1095 mL) while maintaining the temperature between 25-
- 20 30 °C with an ice water bath. The reaction was stirred for 0.5 hours at room temperature then quenched by adding 3N HCl (220 mL). The organic layer was collected, washed with saturated NaHCO₃ and brine, dried over MgSO₄, and
- 25 concentrated in vacuo to give an orange oil (48.22 g). The orange oil was dissolved in 9:1 trifluoroacetic acid/water (100 mL) and stirred for 0.67 hours at room temperature. The

reaction was extracted with ethyl acetate, washed with 10% Na₂CO₃ and brine, dried over MgSO₄, and concentrated in vacuo to give a brown solid which was recrystallized from diethyl ether/hexane to give the benzoin (32.90 g, 52%): mp 118-123 °C. ¹H NMR (CDCl₃) 300 MHz δ 7.90 (d, J=7.1 Hz, 2H) 7.57 (m, 1H) 7.39 (m, 2H) 7.21 (d, J=8.1 Hz, 2H) 7.14 (d, J=7.9 Hz, 2H) 5.93 (s, 1H) 4.50 (br s, 1H) 2.29 (s, 3H).

10 Step 2. Preparation of 2-trifluoromethyl-4-phenyl-5-(4-methylphenyl)oxazole.

Trifluoroacetonitrile (1.57 g (16.5 mmol)) was added to DMF (100 mL). This solution was cooled to 0 °C and 4'-methylbenzoin from Step 1 (3.05 g, 13.5 mmol) was added. DBU (2.51 g, 16.5 mmol) was added and the solution was warmed to 15 room temperature for 4 hours. The reaction was heated to approximately 100 °C for an additional 4 hours. The solution was cooled to room temperature and poured into 400 mL 1N HCl and extracted with 500 mL ethyl acetate. The organics were washed consecutively with 1N HCl (400 mL), NaHCO₃ (saturated) 20 (400 mL) and brine (400 mL), dried over Na₂SO₄ and concentrated. The residue was purified by silica gel chromatography eluting with 5% ether in hexane to give a white solid (1.28 g, 31%): mp 54-55 °C. Anal. Calc'd. for C₁₇H₁₂NOF₃: C, 67.33; H, 3.99; N, 4.62. Found: C, 67.22; 25 H, 3.94; N, 4.55.

Step 3. Preparation of 5-(3-aminosulfonyl-4-methylphenyl)-4-phenyl-2-trifluoromethyloxazole.

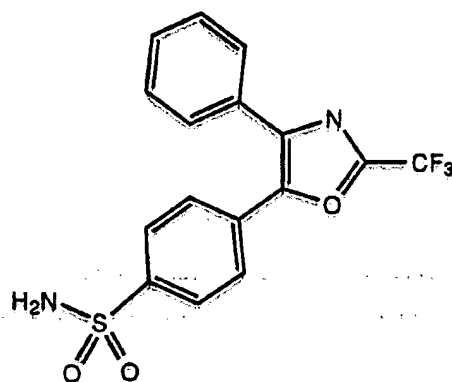
2-Trifluoromethyl-4-phenyl-5-(4-methylphenyl)oxazole 30 from Step 2 (0.34 g) was added to chlorosulfonic acid cooled to 0 °C (12 mL) and the reaction was warmed to room temperature for 1.25 hours. The solution was carefully poured into ice water and extracted with three 75 mL portions of dichloromethane. The combined organics were washed once 35 with brine (75 mL) and stirred over ice cold NH₄OH (125 mL)

151

for 2 hours. The dichloromethane layer was separated, washed consecutively with 1N HCl (2 x 75 mL), NaHCO₃ (saturated) (75 mL) and brine (75 mL), dried over Na₂SO₄ and concentrated.

The crude material was crystallized from ethyl acetate and hexane to yield 2-trifluoromethyl-4-phenyl-5-(3-aminosulfonyl-4-methylphenyl)oxazole (184 mg, 54 %): mp 156-157 °C. Anal. Calc'd, for C₁₇H₁₃N₂O₃SF₃: C, 53.40; H, 3.43; N, 7.33. Found: C, 53.23; H, 3.44; N, 7.31.

10

EXAMPLE 64

15

4-[4-Phenyl-2-trifluoromethyl-5-oxazolyl]benzenesulfonamide**Step 1. Preparation of 2-trifluoromethyl-4,5-diphenyl oxazole.**

Trifluoroacetonitrile (1.58 g, 16.5 mmol) was added to DMF (100 mL). This solution was cooled to 0 °C and benzoin (2.87 g, 13.5 mmol) was added. DBU (2.51 g, 16.5 mmol) was added and the solution was warmed to room temperature for 4 hours. The reaction was heated to approximately 100 °C for an additional 4 hours. The solution was cooled to room temperature and poured into 400 mL 1N HCl and extracted with 500 mL ethyl acetate. The organics were washed consecutively with 1N HCl (400 mL), NaHCO₃ (saturated) (400 mL) and brine (400 mL), dried over Na₂SO₄ and concentrated. The residue

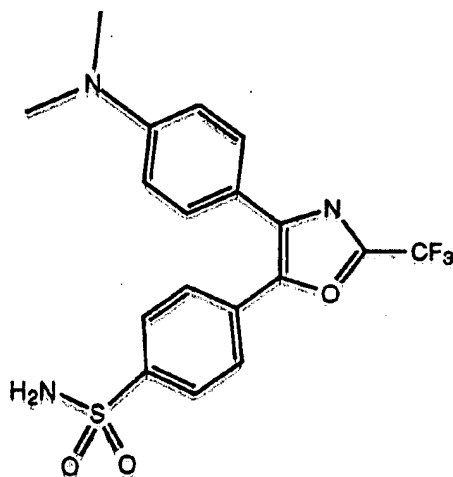
was purified by silica gel chromatography eluting with 5% ether in hexane to give a white solid (1.75 g, 45%): mp 70-71 °C. Anal. Calc'd. for $C_{16}H_{10}NOF_3$: C, 66.44; H, 3.48; N, 4.84. Found: C, 67.33; H, 3.52; N, 4.92.

5

Step 2. Preparation of 4-[4-phenyl-2-trifluoromethyl-5-oxazolyl]benzenesulfonamide.

2-Trifluoromethyl-4,5-diphenyloxazole from Step 1 (0.77g, 2.8 mmol) was added to chlorosulfonic acid (25 mL) 10 (cooled to 0 °C) and the reaction was stirred from 0 °C to room temperature for 5 hours. The solution was carefully poured into ice water and extracted with three 75 mL portions of dichloromethane. The combined organics were washed once with brine (75 mL) and stirred over ice cold NH_4OH (125 mL) 15 for 2 hours. The dichloromethane layer was separated and washed consecutively with 1N HCl (2 x 75 mL), $NaHCO_3$ (saturated) (75 mL) and brine (75 mL), dried over Na_2SO_4 and concentrated. The crude material was crystallized from ethyl acetate and hexane to yield 4-[4-phenyl-2-trifluoromethyl-5-oxazolyl]benzenesulfonamide (0.56 g, 57%): mp 137-138 °C. 20 Anal. Calc'd. for $C_{16}H_{11}N_2O_3SF_3$: C, 52.18; H, 3.01; N, 7.61. Found: C, 52.15; H, 2.98; N, 7.52.

EXAMPLE 65



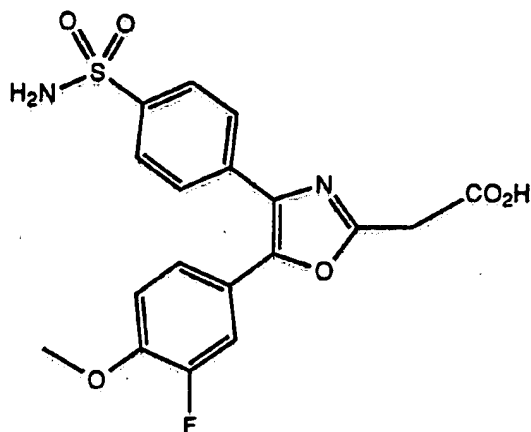
5 4-[4-Dimethylaminophenyl]-2-trifluoromethyl-5-oxazolyl]benzenesulfonamide

Step 1. Preparation of 2-trifluoromethyl-4-(4-dimethylaminophenyl)-5-phenyloxazole.

10 The oxazole was prepared as described in Example 32 with the substitution of 4-dimethylaminobenzoin (3.06 g, 12 mmol) to give a yellow solid (1.84 g, 46%): mp 120-121 °C. Anal. Calc'd. for C₁₈H₁₅N₂OF₃: C, 65.06; H, 4.55; N, 8.43. Found: C, 65.96; H, 4.52; N, 8.42.

15 Step 2. Preparation of 4-[4-Dimethylaminophenyl]-2-trifluoromethyl-5-oxazolyl]benzenesulfonamide

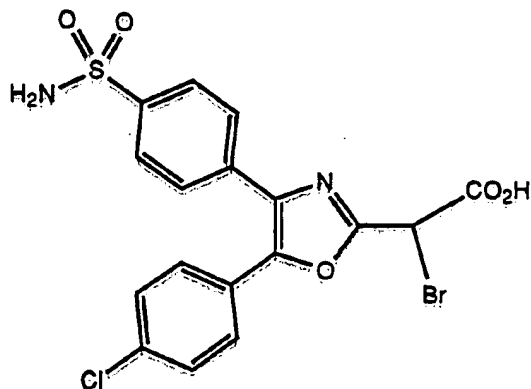
20 Example 33 was prepared from the oxazole of Step 1 as described in Example 32, Step 2 (0.38 g, 62%): mp 159-160 °C. Anal. Calc'd. for C₁₈H₁₆N₃O₃SF₃: C, 52.55; H, 3.92; N, 10.21. Found: C, 52.29; H, 3.98; N, 10.05.

EXAMPLE 66

5 **4-(4-Aminosulfonylphenyl)-5-(3-fluoro-4-methoxyphenyl)-2-oxazoleacetic acid**

Ethyl [4-(4-aminosulfonylphenyl)-5-(3-fluoro-4-methoxyphenyl)]-2-oxazoleacetate (8.7 mg 0.021 mmol) (Example 10 34, Step 4) was dissolved in ethanol (1 mL), and a NaOH solution (2.5 N, 18 ml) was added. The reaction was stirred for 0.25 hours at room temperature at which time HCl (aq., concentrated) was added to acidify the reaction. The aqueous solution was extracted with ethyl acetate (dried over MgSO₄) 15 and concentrated to yield [4-(4-aminosulfonylphenyl)-5-(3-fluoro-4-methoxyphenyl)]-2-oxazoleacetic acid (6.0 mg, 70%):
¹H NMR (CD₃OD) 300 MHz δ 3.91 (s, 3H), 3.97 (s, 2H), 7.19 (t, 1H), 7.31 (m, 2H), 7.76 (d, J=8.7 Hz, 2H), 7.91 (d, J=8.7 Hz, 2H). ¹⁹F NMR (CD₃OD) 282 MHz δ -132.8 (multiplet).

EXAMPLE 67



5 4-[4-Aminosulfonylphenyl]-5-(3-fluoro-4-methoxyphenyl)-2-oxazolyl]α-bromoacetic acid

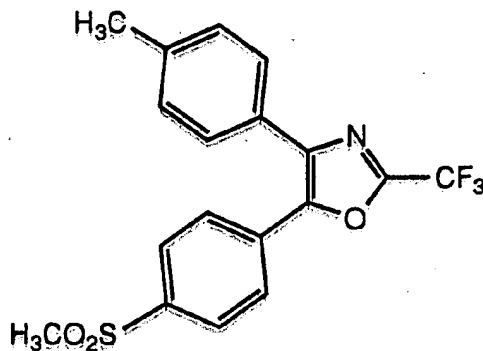
10 [4-(4-Aminosulfonylphenyl)-5-(4-chlorophenyl)-2-oxazolyl]acetic acid (Example 66) (65 mg, 0.165 mmol) was dissolved in chloroform (5 mL) and acetic acid (3 mL). Bromine in acetic acid solution (1.1 M, 0.2 mL) was added and the reaction was stirred for 16 hours. Sodium sulfite was added until the orange color dissipated. 1N HCl (10 mL) was added and the reaction concentrated to dryness. The residue

15 was suspended in acetone (2 mL), filtered through Celite® and concentrated to yield 4-[4-aminosulfonylphenyl]-5-(3-fluoro-4-methoxyphenyl)-2-oxazolyl]α-bromoacetic acid (73 mg, 94%):

¹H NMR (acetone-d₆), 300 MHz δ 4.57 (s, 1H), 6.81 (s, 2H), 7.51 (d, J=8.5 Hz, 2H), 7.64 (d, J=8.5 Hz, 2H), 7.79 (d, J=8.3 Hz, 2H), 7.94 (d, J=8.3 Hz, 2H).

20

EXAMPLE 68



5 4-(4-Methylphenyl)-5-(4-methylsulfonylphenyl)-2-
 trifluoromethyloxazole

Step 1. Preparation of 2-hydroxy-2-(4-methylthiophenyl)-1-
(4-methylphenyl)ethanone.

10 A solution of p-thioanisaldehyde (15.22 g, 100 mmol) and
 zinc iodide (1 g) in dichloromethane (100 mL) was treated
 with a solution of trimethylsilylcyanide (13.3 mL, 100 mmol)
 in dichloromethane (50 mL). The solution was stirred for 0.5
 hours at room temperature, washed with water and saturated
15 NaHCO₃, dried over MgSO₄, and concentrated in vacuo to give
 the trimethylsilyl cyanohydrin as an orange oil (24.9 g).
 The trimethylsilyl cyanohydrin (5.0 g, 20 mmol) was dissolved
 in diethyl ether (50 mL) and added dropwise to a solution of
 p-tolylmagnesium bromide (24 mmol) in diethyl ether (175 mL)
20 while maintaining the temperature at less than 30 °C with an
 ice water bath. The reaction was stirred for 0.25 hours at
 room temperature and then quenched by adding 1N HCl (250 mL).
 The organic layer was collected, washed with saturated NaHCO₃
 and brine, dried over MgSO₄, and concentrated in vacuo to
25 give a yellow solid. The yellow solid was dissolved in 9:1
 trifluoroacetic acid/water (30 mL) and stirred for 0.25 hours
 at room temperature. The reaction was neutralized with
 saturated NaHCO₃ solution, extracted with ethyl acetate,

washed with saturated NaHCO_3 solution and brine, dried over MgSO_4 , and concentrated in vacuo to give a yellow oil. The oil was purified by SiO_2 chromatography eluting with a gradient from 20-30% ethyl acetate in hexane to yield 2-hydroxy-2-(4-methylthiophenyl)-1-(4-methylphenyl)ethanone (2.8 g, 51%): ^1H NMR (CDCl_3) 300 MHz δ 2.36 (s, 3H), 2.43 (s, 3H), 4.54 (d, $J=6.0$ Hz, 1H), 5.89 (d, $J=6.0$ Hz, 1H), 7.20 (m, 6H) 7.80 (d, $J=8.3$ Hz, 2H).

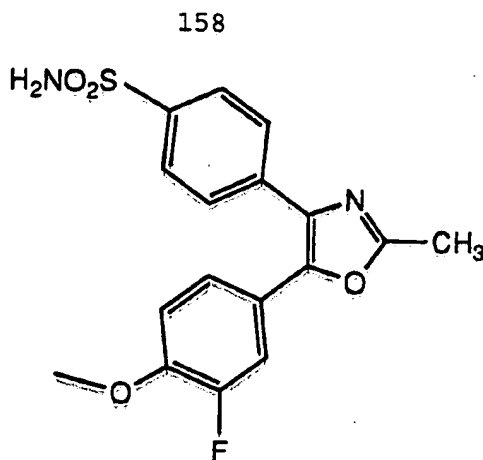
10 Step 2. Preparation of 4-(4-methylphenyl)-5-(4-methylthiophenyl)-2-trifluoromethyl-oxazole.

The oxazole was prepared as in Example 64, Step 1, with the substitution of 2-hydroxy-2-(4-methylthiophenyl)-1-(4-methylphenyl)ethanone to give a white solid (0.6 g, 46%): mp 129-130 °C. Anal. Calc'd. for $\text{C}_{18}\text{H}_{14}\text{NOSF}_3$: C, 61.88; H, 4.04; N, 4.01. Found: C, 61.81; H, 4.09; N, 3.92.

Step 3. 2-trifluoromethyl-4-(4-methylphenyl)-5-(4-methylsulfonylphenyl) oxazole.

20 4-(4-Methylphenyl)-5-(4-methylthiophenyl)-2-trifluoromethyloxazole from Step 2 (350 mg, 1.0 mmol) was dissolved in THF (20 mL), ethanol (20 mL) and water (20 mL). Oxone® (1.2 g, 2 mmol) was added and the reaction stirred for 3 hours. The reaction mixture was filtered and concentrated to dryness. The residue was dissolved in ethyl acetate (200 mL), washed with water, NaHCO_3 and brine, dried and concentrated to yield a white crystalline product (350 mg) which was recrystallized from ethanol and water to yield 4-(4-methylphenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethyl-oxazole (300 mg, 79%): mp 141-142 °C. Anal. Calc'd. for $\text{C}_{18}\text{H}_{14}\text{NO}_3\text{SF}_3$: C, 56.69; H, 3.70; N, 3.67. Found: C, 56.47; H, 3.79; N, 3.57.

EXAMPLE 69



4-[5-(3-Fluoro-4-methoxyphenyl)-2-methyl-4-oxazolyl]benzenesulfonamide

5

Step 1. Preparation of 5-(3-fluoro-4-methoxyphenyl)-2-methyl-4-phenyloxazole.

3-Fluoro-4-methoxybenzoin (Example 34, Step 1) (2.6 g, 10 mmol) and acetic anhydride (1.63 g, 16 mmol) were added to THF (150 mL) and cooled to 0 °C. DBU (1.83 g, 12 mmol) was added and the solution was warmed to room temperature for 16 hours. The reaction was poured into 300 mL 1N HCl and extracted with 500 mL ethyl acetate. The organics were washed consecutively with, NaHCO₃ (saturated) (400 mL) and brine (400 mL) dried over Na₂SO₄ and concentrated. Ammonium acetate (6 g) and acetic acid (100 mL) were added to the acetylated benzoin and the solution was heated to reflux for 2.5 hours. The reaction was concentrated to dryness and the residue dissolved in ethyl acetate (250 mL), washed with 1N HCl, NaHCO₃ and brine, dried and concentrated to yield a crystalline solid (2.37 g, 65%) which was used without further purification.

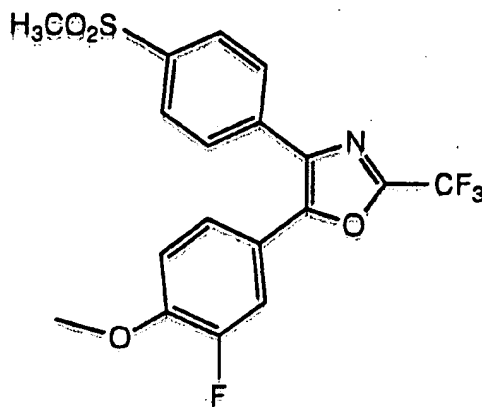
Step 2. Preparation of 5-(3-fluoro-4-methoxyphenyl)-2-methyl-4-oxazolyl]benzenesulfonamide

25

The oxazole of Step 1 was converted to the sulfonamide by the method of Example 64, Step 2 to yield 4-[5-(3-fluoro-

4-methoxyphenyl-2-methyl-4-oxazolyl]benzenesulfonamide (173 mg, 55%): ^1H NMR (acetone d_6), 300 MHz δ 2.52 (s, 3H), 3.96 (s, 3H), 6.61 (s, 2H), 7.24 (m, 1H), 7.37 (m, 2H), 7.81 (d, $J=8.5$ Hz, 2H), 7.90 (d, $J=8.5$ Hz, 2H).

5

EXAMPLE 70

10 5-(3-Fluoro-4-methoxyphenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethyloxazole

Step 1. Preparation of 4-methylthio-3'-fluoro-4'-methoxy benzoin.

15 Magnesium (1.34 g, 55 mmol) was suspended in THF (300 mL) and a solution of 4-bromothioanisole (10.16 g, 50 mmol) in THF (50 mL) was added dropwise over 0.5 hour maintaining the temperature at less than 30 °C. The reaction was stirred an additional 0.5 hour once the addition was complete. 3-
20 Fluoro-p-anisaldehyde silyl cyanohydrin (Example 34, Step 1) (12.7 g, 50 mmol) and diethyl ether (50 mL) were added dropwise to the solution of Grignard at such a rate that the reaction temperature did not rise above 30 °C. Upon complete addition, the reaction was stirred an additional 15 minutes
25 at which time 1N HCl (400 mL) was added and the reaction stirred until all solids were dissolved. The organics were washed with NaHCO_3 (saturated) (400 mL) and brine (400 mL),

dried over Na_2SO_4 and concentrated to yield a mixture of benzoin and silyl benzoin. The crude product was dissolved in $\text{TFA}/\text{H}_2\text{O}$ (9:1) (75 mL) and stirred for 15 minutes. The TFA solution was poured into saturated NaHCO_3 (aq.). The benzoin was extracted with ethyl acetate (350 mL) and washed with NaHCO_3 (saturated) (300 mL) and brine (300 mL). The crude benzoin was crystallized from ethyl acetate and hexane to yield crystals of 4-methylthio-3'-fluoro-4'-methoxybenzoin (4.9 g, 32%): ^1H NMR (CDCl_3) 300 MHz δ 2.45 (s, 3H), 3.81 (s, 3H), 5.8 (s, 1H), 6.86 (m, 1H), 7.01 (m, 2H), 7.17 (d, $J=8.7$ Hz, 2H), 7.79 (d, $J=8.7$ Hz, 2H); ^{19}F NMR (CDCl_3) 282 MHz δ -134.0 (multiplet).

Step 2. Preparation of 2-trifluoromethyl-4-(4-methylthiophenyl)-5-(3-fluoro-4-methoxyphenyl)oxazole.

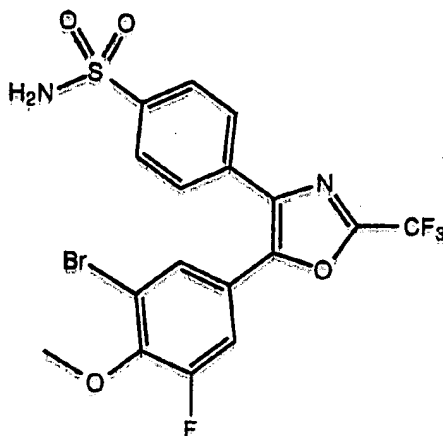
5-(3-Fluoro-4-methoxyphenyl)-4-(4-methylthiophenyl)-2-trifluoromethyloxazole was prepared from the benzoin of Step 1 by the method of Example 64, Step 1. The residue was crystallized from ethanol and water to give a white solid (0.26 g, 50%): ^1H NMR (CDCl_3) 300 MHz δ 2.52 (s, 3H), 3.94 (s, 3H), 6.98 (t, $J=8.7$ Hz, 1H), 7.26 (d, $J=8.5$ Hz, 2H), 7.36 (m, 2H), 7.55 (d, $J=8.5$ Hz, 2H); ^{19}F NMR (CDCl_3) 282 MHz δ -66.6 (s), -134.2 (s).

Step 3. Preparation of 5-(3-fluoro-4-methoxyphenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethyloxazole.

2-Trifluoromethyl-4-(4-methylthiophenyl)-5-(3-fluoro-4-methoxyphenyl)oxazole from Step 2 (38 mg, 0.1 mmol) was converted by the method of Example 68, Step 3 to yield a white crystalline product which was recrystallized from ethanol and water to yield 5-(3-fluoro-4-methoxyphenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethyloxazole (39 mg, 94%): ^1H NMR (CDCl_3) 300 MHz δ 3.1 (s, 3H), 3.96 (s, 3H), 6.98 (t, $J=8.5$ Hz, 1H), 7.36 (m, 2H), 7.88 (d, $J=8.5$ Hz, 2H), 7.98

161

(d, $J=8.5$ Hz, 2H); ^{19}F NMR (CDCl_3) 282 MHz δ -66.6 (s), -133.5 (s). FAB Mass spec. $M + H$ 416.

EXAMPLE 71

4-[5-(3-bromo-4-methoxy-5-fluorophenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide

Step 1. Preparation of 3-bromo-5-fluoro-4-hydroxybenzaldehyde.

A solution of 3-fluoro-p-anisaldehyde (10.40 g, 67.5 mmol) in 1,2-dichloroethane (80 mL) was treated with bromine (3.9 mL, 75.6 mmol) then cooled in ice while adding aluminum chloride (11.87 g, 89.0 mmol). The reaction was stirred for 1.75 hours at room temperature and 1.3 hours at 60 °C. The excess bromine was quenched by adding 10% sodium bisulfite solution. The reaction mixture was extracted with ethyl acetate, washed with 3N HCl, brine, dried over MgSO_4 , and concentrated in vacuo to give a white solid (14.84 g, 100%): mp 136-138 °C. ^1H NMR (acetone- d_6) 300 MHz δ 10.30 (br s, 1H) 9.86 (d, $J=2.0$ Hz, 1H) 7.95 (t, $J=1.6$ Hz, 1H) 7.70 (dd, $J=10.3$ Hz 1.8 Hz, 1H); ^{19}F NMR (acetone- d_6) 282 MHz -133.27 (m). Mass spectrum: $M+H=219/221$.

Step 2. Preparation of 3-bromo-5-fluoro-4-methoxybenzaldehyde.

A solution of 3-bromo-5-fluoro-4-hydroxybenzaldehyde from Step 1 (6.01 g, 27.3 mmol) was treated with methyl iodide (8.89 g, 62.6 mmol) and potassium carbonate (5.79 g, 41.9 mmol). The reaction was stirred for 15.1 hours at 50 °C, filtered and concentrated in vacuo. The residue was dissolved in ethyl acetate, washed with water, 10% sodium hydroxide, and brine. The organic layer was dried over MgSO₄ and concentrated in vacuo to give a brown oil which was crystallized from diethyl ether/hexane to give a white solid (2.63 g, 41%): mp 47-49 °C. ¹H NMR (CDCl₃) 300 MHz δ 9.82 (d, J=2.0 Hz, 1H) 7.85 (t, J=1.6 Hz, 1H) 7.58 (dd, J=11.1 Hz 2.0 Hz, 1H) 4.09 (d, J=3.0 Hz, 3H); ¹⁹F NMR (CDCl₃) 282 MHz -125.92 (m). Mass spectrum: M+H=233/235.

Step 3. Preparation of 3'-bromo-4'-methoxy-5'-fluorobenzoin.

A solution of 3-bromo-5-fluoro-4-hydroxybenzaldehyde from Step 2 (2.63 g, 11.2 mmol) and zinc iodide (0.44 g) in methylene chloride (10 mL) was treated with trimethylsilyl cyanide (1.7 mL, 12.7 mmol). The solution was stirred for 0.6 hours at room temperature, washed with saturated NaHCO₃ and brine, dried over MgSO₄, and concentrated in vacuo to give the trimethylsilyl cyanohydrin as a yellow oil (3.04 g). The trimethylsilyl cyanohydrin was dissolved in diethyl ether (15 mL) and added dropwise to a solution of phenylmagnesium bromide (13.8 mmol) in diethyl ether (90 mL) while maintaining the temperature below 25 °C with an ice water bath. The reaction was stirred for 1.2 hours at room temperature then quenched by adding 3N HCl. The organic layer was collected, washed with saturated NaHCO₃ and brine, dried over MgSO₄, and concentrated in vacuo to give a yellow oil (3.99 g). The yellow oil was dissolved in 9:1 trifluoroacetic acid/water (20 mL) and stirred for 0.33 hours

at room temperature. The reaction was neutralized with solid potassium carbonate, extracted with ethyl acetate, washed with 10% Na₂CO₃ and brine, dried over MgSO₄, and concentrated in vacuo to give the benzoin (3.15 g) as a yellow oil which was used in the next step without further purification.

Step 4. Preparation of 5-(3-bromo-4-methoxy-5-fluorophenyl-4-phenyl)-2-trifluoromethyl-oxazole.

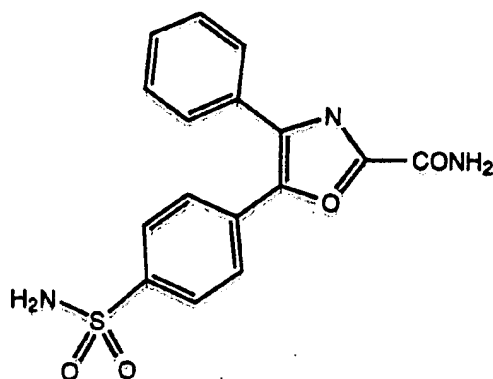
5-(3-Bromo-4-methoxy-5-fluorophenyl-4-phenyl)-2-trifluoromethyloxazole was prepared by the method described in Example 64, Step 1, substituting 3'-bromo-4'-methoxy-5'-fluorobenzoin from Step 3. The crystalline solid residue was recrystallized from ether and hexane to yield analytically pure oxazole (1.9 g, 49%): ¹H NMR (CDCl₃) 300 MHz δ 4.03 (s, 3H), 7.32 (m, 1H), 7.44 (m, 3H), 7.63 (m, 3H); ¹⁹F NMR (CDCl₃) 282 MHz δ -66.6 (s), -126.4 (s).

Step 5. Preparation of 4-[5-(3-bromo-4-methoxy-5-fluorophenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide

The oxazole of Step 4 was reacted as described in Example 64, Step 2. The crude material was chromatographed over SiO₂ eluting with a gradient from 10% - 50% ethyl acetate in hexane to yield 4-[5-(3-bromo-4-methoxy-5-fluorophenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide (0.25 g, 15%): ¹H NMR (CDCl₃) 300 MHz δ 4.05 (s, 3H), 5.18 (s, 2H), 7.28 (m, 1H), 7.61 (m, 1H), 7.80 (d, J=8.5 Hz, 2H), 7.98 (d, J=8.5 Hz, 2H); ¹⁹F NMR (CDCl₃) 282 MHz δ -66.6 (s), -125.7 (s).

EXAMPLE 72

164



5- (4-Aminosulfonylphenyl)-4-phenyloxazole-2-
carboxamide

5

Step 1. Preparation of 4,5-diphenyloxazole-2-acetic acid methyl ester.

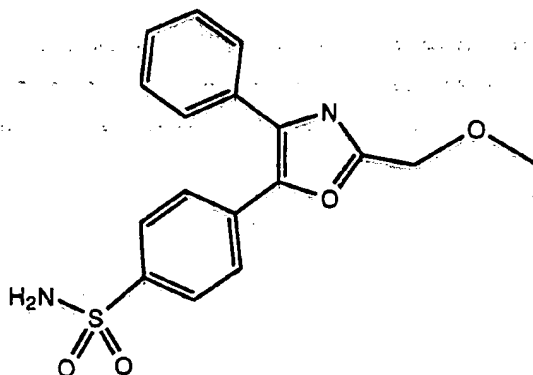
Benzoin (2.12 g, 10 mmol) was dissolved in THF (100 mL) and the solution cooled to 0 °C. Methyl oxalylchloride (1.47 g, 12 mmol) and triethylamine (1.67 mL, 12 mmol) were added and the reaction was warmed to room temperature for 2 hours. Ether (150 mL) was added and the reaction mixture was filtered and concentrated. Ammonium acetate (1.5 g) and acetic acid (150 mL) were added to the acylated benzoin and the solution was heated to reflux for 2.5 hours. The reaction was concentrated to dryness, the residue was dissolved in ethyl acetate (250 mL), washed with water, NaHCO₃ and brine, dried and concentrated to yield a crystalline solid which was chromatographed over SiO₂ eluting with a gradient from 5% - 10% ethyl acetate in hexane to yield the methyl ester (0.79 g, 28%): ¹H NMR (CDCl₃) 300 MHz δ 4.02 (s, 3H), 7.36 (m, 6H), 7.67 (m, 4H).

Step 2. Preparation of 5-(4-aminosulfonylphenyl)-4-phenyloxazole-2-carboxamide.

4,5-Diphenyloxazole-2-acetic acid methyl ester from Step 1 (790 mg, 2.8 mmol) was added to chlorosulfonic acid cooled to 0 °C (25 mL) and the reaction was warmed to room

temperature for 2 hours. The solution was carefully poured into ice water and extracted with three 75 mL portions of dichloromethane. The combined organics were washed once with brine (75 mL) and stirred over ice cold NH_4OH (125 mL) for 2.5 hours. The dichloromethane layer was separated and washed consecutively with 1N HCl (2 x 75 mL), NaHCO_3 (saturated) (75 mL) and brine (75 mL), dried over Na_2SO_4 and concentrated. The crude material was crystallized from a minimum amount of boiling ethyl acetate to yield 5-(4-aminosulfonylphenyl)-4-phenyl-oxazole-2-carboxamide (0.45 g, 46%): ^1H NMR (acetone- d_6) 300 MHz δ 6.73 (broad s, 2H), 7.22 (broad s, 2H), 7.48 (m, 3H), 7.68 (m, 2H), 7.84 (d, $J=8.5$ Hz, 2H), 7.98 (d, $J=8.5$ Hz, 2H). FAB Mass spec. $M + H$ 344.

EXAMPLE 73



20

4-[2-Methoxymethyl-4-phenyl-oxazolyl]benzenesulfonamide

Step 1. Preparation of 2-methoxymethyl-4,5-diphenyloxazole.

Benzoin (2.12 g, 10 mmol) was dissolved in THF (50 mL) and the solution cooled to 0 °C. Methoxy acetylchloride (2.28 g, 21 mmol) and triethylamine (2.12 mL, 21 mmol) were added and the reaction was warmed to room temperature for 32 hours. Ether (150 mL) was added and the reaction was

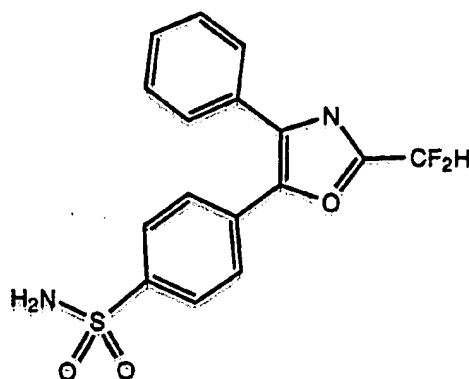
filtered. The organics were washed with 1N HCl, NaHCO₃ and brine, dried over Na₂SO₄ and concentrated. Ammonium acetate (1.32 g, 17.1 mmol) and acetic acid (50 mL) were added to the acylated benzoin and the solution was heated to reflux for 3 hours. The reaction was concentrated to dryness, residue was dissolved in ethyl acetate (250 mL), washed with water, NaHCO₃ and brine, dried and concentrated to yield a crystalline solid (2.1 g) which was recrystallized from ethyl acetate and hexane to yield 2-methoxymethyl-4,5-diphenyloxazole (0.82 g, 36%): ¹H NMR (CDCl₃) 300 MHz δ 3.53 (s, 3H), 4.62 (s, 2H), 7.35 (m, 6H), 7.62 (m, 4H).

Step 2. Preparation of 4-[2-methoxymethyl-4-phenyl-oxazolyl]benzenesulfonamide.

2-Methoxymethyl-4,5-diphenyloxazole from Step 1 (500 mg, 1.9 mmol) was added to chlorosulfonic acid cooled to 0 °C (25 mL) and the reaction allowed was warmed to room temperature for 3 hours. The solution was carefully poured into ice water and extracted with three 75 mL portions of dichloromethane. The combined organics were washed once with brine (75 mL) and stirred over ice cold NH₄OH (125 mL) for 2.5 hours. The dichloromethane layer was separated, washed consecutively with 1N HCl (2 x 75 mL), NaHCO₃ (saturated) (75 mL) and brine (75 mL), dried over Na₂SO₄ and concentrated. The crude material was chromatographed over SiO₂ eluting with a gradient from 50% - 75% ethyl acetate in hexane to yield 4-[2-methoxymethyl-4-phenyl-oxazolyl]benzenesulfonamide (0.22 g, 34%): ¹H NMR (acetone-d₆) 300 MHz δ 3.47 (s, 3H), 4.62 (s, 2H), 6.69 (s, 2H), 7.44 (m, 3H), 7.65 (m, 2H), 7.77 (d, J=8.7 Hz, 2H), 7.93 (d, J=8.7 Hz, 2H). FAB Mass spec. M + H 345.

EXAMPLE 74

167



4-[2-Difluoromethyl-4-phenyl-5-oxazolyl]benzenesulfonamide

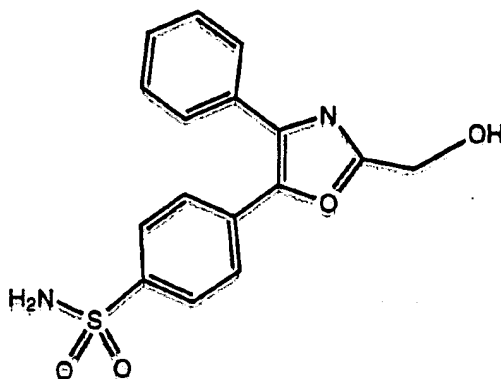
5

Step 1. Preparation of 2-difluoromethyl-4,5-diphenyloxazole.

Difluoroacetic acid was dissolved in ethanol containing NaOH (4 mL, 2.5 N), and concentrated to dryness. The solid was re-dissolved in EtOH (50 mL) and re-concentrated to dryness. The salt was suspended in DMF (30 mL) and desylbromide (2.75 g, 10 mmol) was added. The reaction was stirred for 16 hours and concentrated. The residue was dissolved in ethyl acetate (250 mL), washed with 0.1N HCl (75 mL), NaHCO₃ (saturated) (75 mL) and brine (75 mL), dried over Na₂SO₄ and concentrated to yield 3.09 g of a colorless oil. Ammonium acetate (2.31 g, 30 mmol) and acetic acid (25 mL) were added to the acylated benzoin and the solution was heated to reflux for 3 hours. The reaction was concentrated to dryness, the residue was dissolved in ethyl acetate (250 mL), washed with water, NaHCO₃ and brine, dried and concentrated. The crude product was chromatographed over SiO₂, eluting with a gradient from 1% - 10% ether in hexane, to yield 2-difluoromethyl-4,5-diphenyloxazole (0.35 g, 12%): ¹H NMR (CDCl₃) 300 MHz δ 6.74 (t, J 52.6 Hz, 1H), 7.39 (m, 6H), 7.64 (m, 4H). ¹⁹F NMR (CDCl₃) 282 MHz δ -118.6 (d, J 52.9 Hz). FAB Mass spec. M + H 272.

Step 2. Preparation of 4-[2-difluoromethyl-4-phenyl-5-oxazolyl]benzenesulfonamide

2-Difluoromethyl-4,5-diphenyloxazole from Step 1 (320 mg, 1.18 mmol) was added to chlorosulfonic acid cooled to 0 °C (10 mL) and the reaction was warmed to room temperature for 2 hours. The solution was carefully poured into ice water and extracted with three 75 mL portions of dichloromethane. The combined organics were washed once with brine (75 mL) and stirred over ice cold NH_4OH (125 mL) for 2.5 hours. The dichloromethane layer was separated, washed consecutively with 1N HCl (2 x 75 mL), NaHCO_3 (saturated) (75 mL) and brine (75 mL), dried over Na_2SO_4 and concentrated. The crude material was chromatographed over SiO_2 , eluting with a gradient from 20%-50% ethyl acetate in hexane, to yield 4-[2-difluoromethyl-4-phenyl-5-oxazolyl]benzenesulfonamide (0.26 g, 63%): ^1H NMR (CD_3OD) 300 MHz δ 6.99 (t, J 52.2 Hz, 1H), 7.43 (m, 3H), 7.61 (m, 2H), 7.75 (d, J=6.8 Hz, 2H), 7.93 (d, J=6.8 Hz, 2H). ^{19}F NMR (CD_3OD) 282 MHz δ -121.6 (d, J 52.2 Hz).

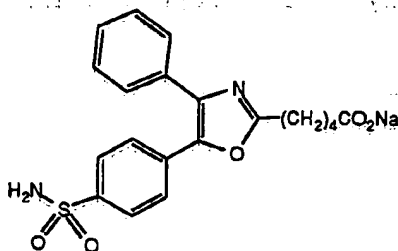
EXAMPLE 75

5 **4-[2-Hydroxymethyl-4-phenyl-5-oxazolyl]benzenesulfonamide**

Deoxybenzoin (10 g, 51 mmol) was added to chlorosulfonic acid cooled to 0 °C (25 mL) and the reaction was warmed to
10 room temperature for 4 hours. The solution was carefully poured into ice water, filtered and the aqueous layer was extracted with three 250 mL portions of dichloromethane. The combined organics were washed once with brine (75 mL) and stirred over ice-cold NH₄OH (125 mL) for 16 hours. The
15 dichloromethane layer was separated and washed consecutively with 1N HCl (2 x 75 mL), NaHCO₃ (saturated) (75 mL) and brine (75 mL), dried over Na₂SO₄ and concentrated. The crude material (4.23 g) was suspended in acetic acid (75 mL) and HBr/HOAc solution (33 u/V% HBr in HOAc, 25 mL) and Br₂ (0.79
20 mL, 15.4 mmol) was added. After 0.25 hours at room temperature the reaction was complete by TLC, and the reaction was concentrated to remove the acetic acid. The residue was dissolved in ethyl acetate (250 mL) and NaHSO₃ (10%, 250 mL). The organics were washed with NaHCO₃
25 (saturated) (75 mL) and brine (75 mL), dried over Na₂SO₄ and concentrated yielding a crude 4-sulfonamido-desylbromide

which was used without purification. Glycolic acid mono sodium salt (1.55 g, 15.8 mmol) and the 4-sulfonamido-desylbromide were suspended in DMF (350 mL) and stirred at room temperature for 16 hours. The reaction was concentrated and the residue, along with ammonium acetate (2.31 g, 30 mmol) and acetic acid (25 mL), were heated to reflux for 3 hours. The reaction was concentrated to dryness. The residue was dissolved in ethyl acetate (250 mL), washed with water, NaHCO₃ and brine, dried and concentrated. The crude product was chromatographed over SiO₂, eluting with a gradient from 50%-75% ethyl acetate in hexane, to yield 4-[2-hydroxymethyl-4-phenyl-5-oxazolyl]benzenesulfonamide: ¹H NMR (acetone-d₆) 300 MHz δ 4.76 (m, 2H), 6.68 (s, 2H), 7.45 (m, 3H), 7.65 (m, 2H), 7.77 (d, J=6.8 Hz, 2H), 7.94 (d, J=8.7 Hz, 2H).

Example 76



5-[(4-Aminosulfonyl)phenyl]-4-phenyloxazole-2-pentanoic acid, sodium salt.

Step 1: Preparation of 2-[(4-chlorosulfonyl)phenyl]-1-phenylethanone

Deoxybenzoin (10 g, 0.051 mol) was added in portions to neat chlorosulfonic acid (50 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 2 h, then warmed to room temperature and stirred at room temperature for 1.5 h. The reaction mixture was cooled to -78 °C and was carefully poured onto crushed ice. The resulting solid was collected by filtration, washed with water, and dried to give 10.3 g (68.5%) of the desired sulfonyl chloride as a yellow solid.

This crude material was used for the next reaction without further purification: HRMS: (calcd for $C_{14}H_{11}O_3SCl$ 295.0196) 295.0205.

5 Step 2: Preparation of 2-[(4-aminosulfonyl)phenyl]-1-phenylethanone

A solution of the sulfonyl chloride from Step 1 (9 g, 0.03 mol) in tetrahydrofuran (100 mL) was slowly added to ammonium hydroxide (100 mL) at 5 °C. The reaction mixture
10 was stirred first for 1.5 h at 5 °C and then for 30 minutes at room temperature. The resulting solid was collected by filtration, washed with excess water and hexane, and vacuum dried to give 3.47 g (41.3%) of the desired sulfonamide as a white solid: m.p. 259-261.5 °C, 1H -NMR (DMSO- d_6 /300 MHz) δ
15 4.52 (s, 2H), 7.30 (s, 2H), 7.43 (bd, 2H, J = 8.26 Hz), 7.54 (dd, 2H, J = 7.56 Hz), 7.65 (dd, 1H, J = 7.35 Hz), 7.75 (d, 2H, J = 8.26 Hz), 8.04 (d, 2H, J = 7.45 Hz). HRMS (calcd for $C_{14}H_{13}NO_3S$ 276.0694) 276.0709.

20 Step 3: Preparation of 2-bromo-2-[(4-aminosulfonyl)phenyl]-1-phenylethanone

The sulfonamide from Step 2 (5.0 g, 0.018 mol) was suspended in dichloroethane (50 mL), then a solution of 30% HBr in acetic acid (20 mL), acetic acid (70 mL) and bromine
25 (1 mL) was added at room temperature. The reaction mixture was stirred for 40 minutes at room temperature and then was concentrated in vacuo. Water (200 mL) was added to the resulting concentrated residue, and the mixture was extracted with ethyl acetate (2 x 250 mL). The combined ethyl acetate
30 extracts were washed with 5% sodium bicarbonate (2 x 250 mL), and brine (2 x 250 mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure. Methylene chloride (50 mL) was added to the concentrated residue, and a solid precipitated. This solid was collected by filtration,
35 washed with cold methylene chloride and air-dried to give 3.5 g (54.9%) of 2-bromo-2-[(4-aminosulfonyl)phenyl]-1-phenylethanone as a yellow solid: m.p. 153.6-155 °C. 1H -NMR

(DMSO- d_6 /300 MHz) δ 7.25 (s, 1H), 7.38 (s, 2H), 7.54 (dd, 2H, J = 7.55 Hz), 7.62-7.74 (m, 3H), 7.82 (d, 2H, J = 8.46 Hz), 8.07 (d, 2H, J = 8.66 Hz). HRMS (calcd for $C_{14}H_{12}NO_3SBr$ 353.9800) 353.9824.

5

Step 4: Preparation of methyl 5-[(4-aminosulfonyl)phenyl]-4-phenyloxazole-2-pentanoate

An aqueous solution of 2.5N NaOH (2.3 mL, 5.65 mmol) was added to adipic acid monomethyl ester (0.9 g, 5.65 mmol) in ethanol (10 mL), and the mixture was stirred for 15 min at room temperature. The solvents were removed at reduced pressure. Several mL of absolute ethanol were added to the concentrated residue, and the mixture was again concentrated at reduced pressure. This procedure was repeated three times until a white solid formed, which was dried under high vacuum. The resulting carboxylic acid sodium salt was suspended in 10 mL of anhydrous DMF. The bromoketone (2 g, 5.65 mmol) from Step 3 was dissolved in 10 mL of anhydrous DMF and added at room temperature to the DMF solution of the sodium carboxylate. The reaction mixture was stirred for 18 h at room temperature, and then the DMF was removed at reduced pressure. Ethyl acetate (100 mL) was added to the concentrated residue, and the mixture was filtered. The filtrate was concentrated and dried to give the desired crude α -acyloxy ketone. Acetic acid (10 mL) and ammonium acetate (1.32 g, 17.1 mmol) were added to this concentrated residue, and this mixture was heated at 100 °C for 3 h. The reaction mixture was cooled to room temperature, and the excess acetic acid was removed under vacuum. The resulting residue was partitioned between water (100 mL) and ethyl acetate (200 mL). The organic layer was separated, washed with saturated aqueous sodium bicarbonate (2 x 100 mL), saturated brine (1 x 100 mL), dried over magnesium sulfate, filtered and concentrated. The concentrated residue was purified by flash chromatography on silica gel (eluting with 4:1 ethyl acetate:hexane) to give 0.73 g of a white solid which was recrystallized from methylene chloride and hexane to give

0.48 g (21%) of methyl 5-[(4-aminosulfonyl)phenyl]-4-phenyloxazole-2-pentanoate as a white solid: m.p. 165.8-167.3 °C. ¹H-NMR (CDCl₃/300 MHz) 1.78-1.89 (m, 4H), 2.40 (t, 2H, J = 7.25 Hz), 2.90 (t, 2H, 7.35 Hz), 3.68 (s, 3H), 4.85 (s, 2H), 7.37-7.42 (m, 3H), 7.58-7.61 (m, 2H), 7.71 (d, 2H, J = 8.66 Hz), 7.88 (d, 2H, J = 8.66 Hz). HRMS (calcd for C₂₁H₂₂N₂O₅S 414.1249) 414.1259.

10 Step 5: Preparation of 5-[(4-aminosulfonyl)phenyl]-4-phenyloxazole-2-pentanoic acid

Methyl 5-[(4-aminosulfonyl)phenyl]-4-phenyloxazole-2-pentanoate (1.48 g, 3.57 mmol) (Step 4) and LiOH (0.45 g, 0.011 mmol) were dissolved in 1:1 tetrahydrofuran/methanol (90 mL) containing 3 mL of water. The resulting mixture was stirred for 48 h at room temperature. The solvents were removed at reduced pressure, and the concentrated residue was partitioned between ethyl acetate (150 mL) and 1 N HCl (150 mL) in a separatory funnel and shaken vigorously. The organic layer was separated and washed with saturated brine (1 x 150 mL), dried over magnesium sulfate, filtered and concentrated. The concentrated residue was vacuum dried to give 1.03 g (72%) of 5-[(4-aminosulfonyl)phenyl]-4-phenyloxazole-2-pentanoic acid as a white solid: mp. 157.2-159.0 °C. ¹H-NMR (CD₃OD/300 MHz) 1.70-1.80 (m, 2H), 1.86-1.94 (m, 2H), 2.38 (t, 2H, J = 7.25 Hz), 2.93 (t, 2H, J = 7.35 Hz), 7.42-7.45 (m, 3H), 7.55-7.58 (m, 2H), 7.69 (d, 2H, J = 8.66 Hz), 7.87 (d, 2H, J = 8.66 Hz). HRMS (calcd for C₂₀H₂₀N₂O₅S 400.1093) 400.1087.

30 Step 6: Preparation of 5-[(4-aminosulfonyl)phenyl]-4-phenyloxazole-2-pentanoic acid, sodium salt

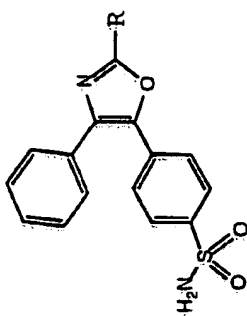
5-[(4-aminosulfonyl)phenyl]-4-phenyloxazole-2-pentanoic acid (Step 5) (0.19 g, 0.47 mmol) was dissolved in 3 mL of ethanol. 2.5 N Sodium hydroxide (2.4 mL, 0.47 mmol) was added, and the solution was stirred for 5 min. at room temperature. The solvents were removed, several mL of absolute ethanol were added to the concentrated residue, and

the mixture was again concentrated at reduced pressure. This procedure was repeated twice until a white solid formed, which was dried under high vacuum to give 0.19 g (96%) of 5-[(4-aminosulfonyl)phenyl]-4-phenyloxazole-2-pentanoic acid, sodium salt as a white solid: m.p. >250 °C. ¹H NMR(CD₃OD/300 MHz) 1.70-1.80 (m, 2H), 1.86-1.93 (m, 2H), 2.25 (t, 2H, J = 7.35 Hz), 2.93 (t, 2H, J = 7.45 Hz), 7.41-7.44 (m, 3H), 7.55-7.58 (m, 2H), 7.70 (d, 2H, J = 8.86 Hz), 7.88 (d, 2H, J = 8.66 Hz). HRMS (calcd for C₂₀H₁₉N₂O₅Na 423.0991) 423.0991.

10

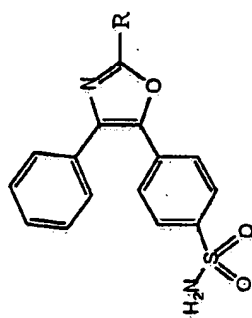
Other representative examples prepared by similar methods from 2-bromo-2-[(4-aminosulfonyl)phenyl]-1-phenyl-ethanone are summarized in Table 1.

TABLE 1



Example No.	R	m.p. (°C)	Analyses
77	-(CH ₂) ₃ CO ₂ CH ₃	147.7-150.1	HRMS: Calcd. 400.1093 HRMS: Found 400.1073
78	-(CH ₂) ₃ CO ₂ H	186.2-190.8	HRMS: Calcd. 387.1015 HRMS: Found 387.1009
79	-CH ₂ OCH ₂ CO ₂ H	ND	HRMS: Calcd. 389.0807 HRMS: Found 389.0821
80	-CH ₂ C(CH ₃) ₂ CH ₂ CO ₂ H	187-192	Calcd. C, 60.86; H, 5.35; N, 6.76 Obs. C, 60.79; H, 5.33; N, 6.68 HRMS: Calcd. 415.1328 HRMS: Found 415.1322
81	-(CH ₂) ₅ CO ₂ CH ₃	74.6-79.4	HRMS: Calcd. 429.1484 HRMS: Found 429.1479
82	-(CH ₂) ₅ CO ₂ H	152.8-154.8	HRMS: Calcd. 415.1328 HRMS: Found 415.1345
83	-(CH ₂) ₃ PO(OCH ₂ CH ₃) ₂	128.8-133.5	HRMS: Calcd. 497.1406 HRMS: Found 497.1414
84	-(CH ₂) ₃ PO ₃ H ₂	193.6-199.2	HRMS: Calcd. 423.0780 HRMS: Found 423.0772
85	-CH ₂ PO(OCH ₂ CH ₃) ₂	89.2-100.5	HRMS: Calcd. 450.1014 HRMS: Found 450.0997
86	-CH ₂ PO(OCH ₂ CH ₃)OH	ND	HRMS: Calcd. 423.0780 HRMS: Found 423.0791

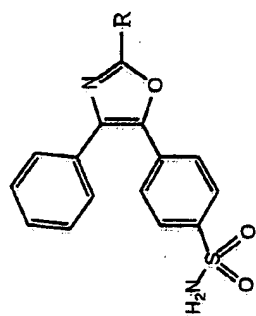
TABLE 1 (Continued)



5

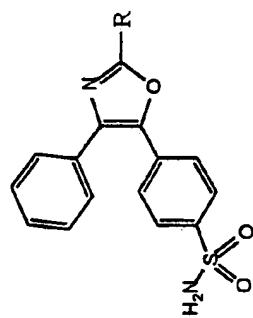
Example No.	R	m.p. (°C)	Analyses	
87	-CH ₂ SO ₂ (CH ₂) ₂ CO ₂ H	71-76	HRMS: Calcd.	451.0634
88	-(CH ₂) ₂ SCH ₂ CO ₂ CH ₃	161-162	HRMS: Found	451.0637
89	-(CH ₂) ₂ SCH ₂ CO ₂ H	41-50	HRMS: Calcd.	433.0892
90	-CH ₂ SCH ₂ CO ₂ C(CH ₃) ₃	46-58	HRMS: Found	433.0912
91	-CH ₂ SCH ₂ CO ₂ H	52-58	HRMS: Calcd.	419.0735
92	-CH ₂ CH(CH ₃)CH ₂ CO ₂ CH ₃	101-102	HRMS: Found	419.0752
93	-CH ₂ CH(CH ₃)CH ₂ CO ₂ H	176-177	HRMS: Calcd.	461.1205
94	-(CH ₂) ₅ CN	oil	HRMS: Found	461.1193
			HRMS: Calcd.	405.0579
			HRMS: Found	405.0560
			HRMS: Calcd.	415.1328
			HRMS: Found	415.1344
			HRMS: Calcd.	401.1171
			HRMS: Found	401.1201
			HRMS: Calcd.	395.1304
			HRMS: Found	395.1287

TABLE 1 (Continued)



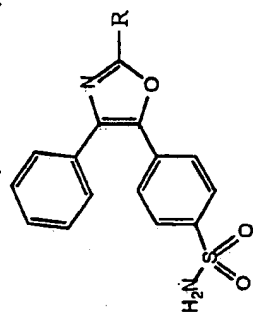
Example No.	R	m.p. (°C)	Analyses
95		oil	HRMS: Calcd. 439.1552 HRMS: Found 439.1531
96		117.3-120.4	HRMS: Calcd. 438.1124 HRMS: Found 438.1134
97		170.1-175.3	HRMS: Calcd. 424.0958 HRMS: Found 424.0967
98		222-225 (d)	HRMS: Calcd. 452.1280 HRMS: Found 452.1280

TABLE 1 (Continued)



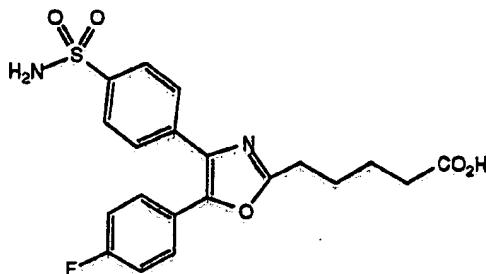
Example No.	R	m.p. (°C)	Analyses	
99		> 290 (d)	HRMS: Calcd. 424.0967 HRMS: Found 424.0967	
100		81-85	HRMS: Calcd. 441.1597 HRMS: Found 441.1593	
101	$-(\text{CH}_2)_3\text{NH}\text{SO}_2\text{CH}_2\text{CO}_2\text{CH}_3$	42-47	HRMS: Calcd. 494.1056 HRMS: Found 494.1052	
102	$-(\text{CH}_2)_2\text{CH}(\text{NH}_2)\text{CO}_2\text{H}$	122-129	HRMS: Calcd. 402.1124 HRMS: Found 402.1140	
103	$-\text{C}\equiv\text{CH}$	182-183	HRMS: Calcd. 325.0647 HRMS: Found 325.0644	
104	$-\text{C}\equiv\text{C}-\text{CH}_3$	172-173	HRMS: Calcd. 339.0803 HRMS: Found 339.0800	

TABLE 1 (Continued)



Example No.	R	m.p. (°C)	Analyses	
105	-CH ₂ NHCO ₂ CH ₂ C ₆ H ₅	152-154	HRMS: Calcd.	464.1280
			HRMS: Found	464.1260
106	-(CH ₂) ₂ NHCO ₂ CH ₂ C ₆ H ₅	70-77	HRMS: Calcd.	478.1437
			HRMS: Found	478.1412
107	-(CH ₂) ₃ NHCO ₂ CH ₂ C ₆ H ₅	54-58	HRMS: Calcd.	492.1593
			HRMS: Found	492.1615
108	-(CH ₂) ₂ N(CH ₃)CO ₂ CH ₂ C ₆ H ₅	50-55	HRMS: Calcd.	492.1593
			HRMS: Found	492.1581
109	-(CH ₂) ₂ NH ₂ • HOAC	181-185	HRMS: Calcd.	344.1069
			HRMS: Found	344.1048
110	-(CH ₂) ₃ NH ₂ • CF ₃ CO ₂ H	178-186		
111	-(CH ₂) ₂ CH(NHCO ₂ CH ₂ C ₆ H ₅)CO ₂ H	75-82	HRMS: Calcd.	536.1491
			HRMS: Found	536.1482
112	-(CH ₂) ₂ N	75.5-81.0	HRMS: Calcd.	412.1695
			HRMS: Found	412.1701
113	-CH ₂ N	75-90	HRMS: Calcd.	383.1304
			HRMS: Found	383.1296
114	-CH ₂ OCH(CH ₂ OH) ₂	60-75	HRMS: Calcd.	405.1120
			HRMS: Found	405.1090

Example 115



5 4-[(4-Aminosulfonyl)phenyl]-5-(4-fluorophenyl)oxazole-
2-pentanoic acid

Step 1: Preparation of 2-(4-fluorophenyl)-2-hydroxy-1-phenylethanone

4-Fluorobenzaldehyde (25 g, 0.2 mol) and zinc iodide (0.14 g, 0.4 mmol) were mixed with 100 mL of methylene chloride. Trimethylsilyl cyanide (20.6 g, 0.21 mol) was dissolved in 30 mL of methylene chloride and added over 30 minutes. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with 200 mL of methylene chloride, and the organic phase was washed with saturated aqueous sodium bicarbonate (1 x 150 mL), saturated brine (1 x 150 mL), dried over magnesium sulfate, filtered, concentrated and vacuum dried to give 47.3 g of the desired trimethylsilyl cyanohydrin as a yellow liquid.

The trimethylsilyl cyanohydrin (45 g, 0.2 mol) was diluted with 100 mL of ether and added to a solution of phenylmagnesium bromide (72 mL of 3.0 M solution in ether, 0.215 mol) in 600 mL of diethyl ether over 1.5 h at room temperature. The reaction mixture was stirred for 3 h at room temperature and slowly quenched with 3 N HCl (300 mL). The organic layer was separated and washed with saturated sodium bicarbonate (1 x 300 mL), saturated brine (1 x 300 mL), dried over magnesium sulfate, filtered, concentrated, and vacuum dried to give 43.2 g of a brown oil. This oil was treated with 150 mL of 9:1 trifluoroacetic acid in water for

3 h at room temperature. Excess saturated aqueous sodium carbonate was slowly added to the reaction mixture, followed by water (200 mL). The aqueous solution was extracted with ether (2 x 200 mL). The combined organic layers were washed with saturated sodium bicarbonate (1 x 200 mL), saturated brine (1 x 200 mL), dried over magnesium sulfate, filtered and concentrated. The crude material was crystallized from ethyl acetate and hexane to give 17.4 g (38%) of 2-(4-fluorophenyl)-2-hydroxy-1-phenylethanone as a yellow solid: m.p. 91-94 °C. HRMS (calcd for C₁₄H₁₁FO₂ 231.0831) 231.0835.

Step 2 Preparation of methyl 4-[(4-aminosulfonyl)phenyl]-5-(4-fluorophenyl)oxazole-2-pentanoate

5-(Methoxycarbonyl)pentanoyl chloride (6.5 g, 0.036 mol) in 10 mL of methylene chloride and triethylamine (7.1 g, 0.07 mol) was added to 2-(4-fluorophenyl)-2-hydroxy-1-phenylethanone (Step 1) (8 g, 0.035 mol) in 100 mL of methylene chloride. The resulting mixture was stirred for 2 h at room temperature, diluted with 200 mL of methylene chloride, washed with water (1 x 100 mL), and saturated brine (1 x 100 mL), dried over magnesium sulfate, filtered and concentrated. The concentrated residue was dried under vacuum to give 12.2 g of crude ester intermediate. Acetic acid (50 mL) and ammonium acetate (10.2 g, 0.132 mol) were added to this ester intermediate (12.2 g, 0.033 mol). The resulting mixture was heated for 3 h at 100 °C. The reaction mixture was cooled to room temperature, and the excess acetic acid was removed under vacuum. The resulting residue was partitioned between water (150 mL) and ethyl acetate (300 mL). The organic layer was separated, washed with saturated aqueous sodium bicarbonate (2 x 150 mL), saturated brine (2 x 150 mL), dried over magnesium sulfate, filtered and concentrated. The concentrated residue was purified by flash chromatography on silica gel (eluting with 1: 9 ethyl acetate:hexane) to give 7 g (60%) of pure methyl 4-(phenyl)-5-(4-fluorophenyl)oxazole-2-pentanoate as a yellow oil.

Chlorosulfonic acid (38.6 g, 0.33 mol) was slowly added to methyl 4-(phenyl)-5-(4-fluorophenyl)oxazole-2-pentanoate (4.7 g, 0.013 mol) at 5 °C. The ice bath was removed, and the reaction mixture was stirred for 3 h at room temperature.

5 The reaction mixture was diluted with methylene chloride (200 mL) and poured slowly into ice. The organic layer was separated and added to ammonium hydroxide (50 mL) at room temperature. The reaction mixture was stirred for 30 minutes at room temperature. The organic layer was separated and

10 washed with water (1 x 200 mL), brine (1 x 200 mL), dried over magnesium sulfate, filtered and concentrated. The concentrated residue was purified by flash chromatography on silica gel (eluting with 9:11 ethyl acetate:hexane) to give 0.74 g (13%) of methyl 4-[(4-aminosulfonyl)phenyl]-5-(4-

15 fluorophenyl)-oxazole-2-pentanoate as a pale yellow solid: m.p. 82.4-87.4 °C. ¹H NMR (CDCl₃/300 MHz) 1.74-1.95 (m, 4H), 2.40 (t, 2H, J = 7.25 Hz), 2.88 (t, 2H, J = 7.35 Hz), 3.67 (s, 3H), 4.93 (bs, 2H), 7.07-7.13 (m, 2H), 7.50-7.55 (m, 2H), 7.75 (d, 2H, J = 8.66 Hz), 7.89 (d, 2H, J = 8.66 Hz). ¹⁹F NMR

20 (CDCl₃/300 MHz) -111.22 to -111.127 ppm. HRMS (calcd for C₂₁H₂₁N₂O₅S 433.1233) 433.1209.

Step 3: Preparation of 4-[(4-aminosulfonyl)phenyl]-5-(4-fluorophenyl)-oxazole-2-pentanoic acid

25 Methyl 4-[(4-aminosulfonyl)phenyl]-5-(4-fluorophenyl)oxazole-2-pentanoate (Step 2) (0.51 g, 1.2 mmol) was dissolved in 30 mL of 1:1 THF/methanol. Lithium hydroxide (0.2 g, 4.7 mmol) and 1 mL of water were added. The reaction mixture was stirred for four days at room

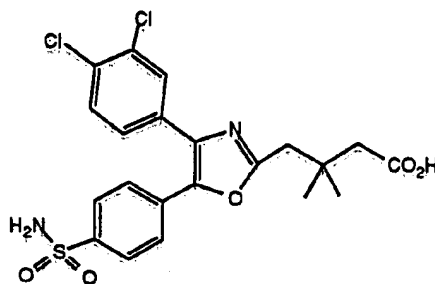
30 temperature, then the solvents were removed at reduced pressure. The concentrated residue was partitioned between ethyl acetate (100 mL) and 3 N HCl (100 mL) in a separatory funnel and shaken vigorously. The organic layer was separated and washed with saturated brine (1 x 100 mL), dried

35 over magnesium sulfate, filtered and concentrated. The concentrated residue was crystallized from ethyl acetate and hexane to give 0.4 g (81%) of 4-[(4-aminosulfonyl)phenyl]-5-

183

(4-fluorophenyl)oxazole-2-pentanoic acid as a white solid:
 m.p. 153-154.5 °C. ¹H NMR (CD₃OD/300 MHz) 1.69-1.79 (m, 2H),
 1.85-1.95 (m, 2H), 2.38 (t, 2H, J = 7.15 Hz), 2.91 (t, 2H, J
 = 7.35 Hz), 7.14-7.20 (m, 2H), 7.55-7.60 (m, 2H), 7.73 (d,
 5 2H, J = 8.66 Hz), 7.90 (d, 2H, J = 8.46 Hz). ¹⁹F NMR
 (CD₃COOD/300 MHz) -113.73 to -113.63 ppm. HRMS (calcd for
 C₂₀H₁₉N₂O₅FS 419.1077) 419.1083.

Example 116



5-[(4-Aminosulfonyl)phenyl]-4-(3,4-dichlorophenyl)-
 β,β-dimethyloxazole-2-butanoic acid

Step 1: Preparation of methyl 5-(phenyl)-4-(3,4-dichlorophenyl)-β,β-dimethyloxazole-2-butanoate

2-Bromo-2-(phenyl)-1-(3,4-dichlorophenyl)ethanone (3.00 g, 8.72 mmol), monomethyl 3,3-dimethylglutarate (3.0 g, 17.22 mmol), and powdered anhydrous potassium carbonate (1.79 g, 12.97 mmol) were mixed at room temperature in dimethylformamide (40 mL) for 15 min. The dimethyl-formamide solution was poured into ethyl acetate (200 mL). This solution was extracted with water (2 x 100 mL), 10% aqueous hydrochloric acid (2 x 100 mL), and finally extensively extracted with saturated aqueous ammonium chloride (6 x 100 mL). The ethyl acetate layer was dried over anhydrous sodium sulfate, and the solvent was removed at reduced pressure. The resulting residue was purified by preparative silica gel chromatography to give 2.78 g (73%) of the desired α-acyloxyketone as a light yellow oil: ¹H NMR (CDCl₃/300 MHz) 1.16 (s, 6H), 2.48 (s, 2H), 2.58 (AB, 2H, J_{ab} = 15.0 Hz, Δν =

26.0 Hz), 3.61 (s, 3H), 6.70 (s, 1H), 7.38-7.42 (m, 5H), 7.47 (d, 1H, $J = 8.1$ Hz), 7.73 (dd, 1H, $J = 8.1$ Hz, $J = 2.0$ Hz), 8.01 (d, 1H, $J = 2.0$ Hz). FABMS $m/z = 437$ ($m+H^+$). HRMS (calcd for $C_{22}H_{22}O_5Cl_2$ 437.0923) 437.0905.

5 The α -acyloxyketone (2.53 g, 5.78 mmol) and ammonium acetate (2.53 g, 32.8 mmol) were heated to reflux in acetic acid (40 mL) for 8 h. The solution was poured into ethyl acetate (200 mL) and extracted with water (2 x 200 mL), saturated sodium bicarbonate (2 x 200 mL), and finally
10 saturated aqueous ammonium chloride (1 x 200 mL). The ethyl acetate layer was dried over anhydrous sodium sulfate, and the solvent was removed at reduced pressure. The resulting residue was purified by preparative silica gel chromatography to give 1.57 g (65%) of methyl 5-(phenyl)-4-(3,4-dichloro-
15 phenyl)- β,β -dimethyloxazole-2-butanoate as a yellow oil: 1H NMR ($CDCl_3$ /300 MHz) 1.10 (s, 6H), 2.44 (s, 2H), 2.95 (s, 2H), 3.67 (s, 3H), 7.37-7.56 (m, 7H), 7.79 (d, 1H, $J = 1.8$ Hz). FABMS $m/z = 418$ ($m+H^+$). HRMS (calcd for $C_{22}H_{22}Cl_2NO_3$ 418.0977) 418.0969.

20

Step 2: Preparation of methyl 5-[(4-aminosulfonyl)phenyl]-4-(3,4-dichlorophenyl)- β,β -dimethyloxazole-2-butanoate

Methyl 5-(phenyl)-4-(3,4-dichlorophenyl)- β,β -dimethyloxazole-2-butanoate (Step 1) (980.0 mg, 2.34 mmol)
25 was cooled to $-25^\circ C$ in a dry ice/methanol bath. Chlorosulfonic acid (15.0 mL) was added, and the solution was warmed to room temperature over 1 h. The solution was stirred for 6 h and slowly poured directly into ice (300 mL in a 500 mL Erlenmeyer flask). The resulting heterogeneous
30 aqueous solution was poured into ethyl acetate (200 mL). The ethyl acetate layer was collected, extracted with water (1 x 100 mL) and mixed with ammonium hydroxide solution (50 mL) for 30 min. The ethyl acetate was collected, extracted with saturated aqueous ammonium chloride (2 x 100 mL), dried over
35 sodium sulfate and concentrated *in vacuo* to give 924 mg (79%) of methyl 5-[(4-aminosulfonyl)-phenyl]-4-(3,4-dichlorophenyl)- β,β -dimethyloxazole-2-butanoate as a foam:

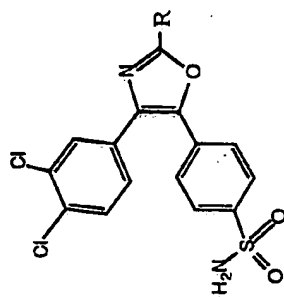
m.p. 54-57 °C. ¹H NMR (CDCl₃/300 MHz) 1.19 (s, 6H), 2.45 (s, 2H), 2.99 (s, 2H), 3.68 (s, 3H), 4.89 (bs, 2H), 7.42-7.48 (m, 2H), 7.69 (d, 2H, J = 8.5 Hz), 7.76 (d, 1H, J = 1.7 Hz), 7.92 (d, 2H, J = 8.5 Hz). FABMS m/z = 497 (m+H⁺). HRMS (calcd for C₂₂H₂₂Cl₂N₂O₅S 497.0705) 497.0681.

Step 3: Preparation of 5-[(4-aminosulfonyl)phenyl]-4-(3,4-dichlorophenyl)-β,β-dimethyloxazole-2-butanoic acid

Methyl 5-[(4-aminosulfonyl)phenyl]-4-(3,4-dichlorophenyl)-β,β-dimethyloxazole-2-butanoate (Step 2) (165.0 mg, 0.33 mmol) and lithium hydroxide mono hydrate (15.0 mg, 0.36 mmol) were mixed in tetrahydrofuran-methanol-water (5.0 mL, 7:2:1) and stirred at room temperature for 16 h. The solution was acidified with 10% aqueous hydrochloric acid (pH = 1) and poured into ethyl acetate (50 mL). The organic layer was extracted with brine (2 x 25 mL), dried over sodium sulfate and concentrated at reduced pressure to give 140 mg (87%) of 5-[(4-aminosulfonyl)phenyl]-4-(3,4-dichlorophenyl)-β,β-dimethyloxazole-2-butanoic acid as a foam: m.p. 82-85 °C. ¹H NMR (CD₃OD/300 MHz) 1.20 (s, 6H), 2.41 (s, 2H), 3.02 (s, 2H), 7.53 (dd, 1H, J = 8.4 Hz, J = 2.1 Hz), 7.57 (d, 1H, J = 8.4 Hz), 7.72 (d, 2H, J = 8.7 Hz), 7.78 (d, 1H, J = 2.1 Hz), 7.94 (d, 2H, J = 8.7 Hz). FABMS m/z = 483 (m+H⁺). HRMS (calcd for C₂₁H₂₀Cl₂N₂O₅S 483.0548) 483.0522.

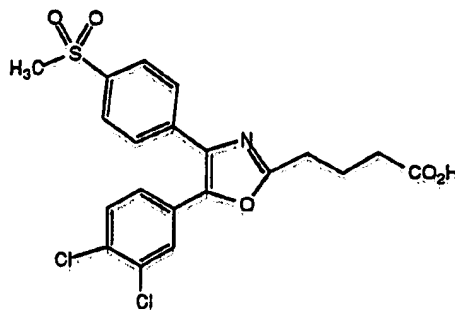
Other representative examples prepared by similar methods from 2-bromo-2-(phenyl)-1-(3,4-dichlorophenyl)-ethanone are summarized in Table 2.

TABLE 2



Example No.	R	m.p. (°C)	Analyses	
117	-(CH ₂) ₂ CO ₂ CH ₃	215.7-217.1	HRMS: Calcd.	455.0235
			HRMS: Found	455.0239
118	-(CH ₂) ₂ CO ₂ H	190-192	HRMS: Calcd.	441.0079
			HRMS: Found	441.0093
119	-(CH ₂) ₃ CO ₂ CH ₃	231.5-232.5	HRMS: Calcd.	469.0392
			HRMS: Found	469.0395
120	-(CH ₂) ₃ CO ₂ H	146-151	HRMS: Calcd.	445.0235
			HRMS: Found	445.0229
121	-(CH ₂) ₄ CO ₂ CH ₃	115-118	HRMS: Calcd.	483.0548
			HRMS: Found	483.0534
122	-(CH ₂) ₄ CO ₂ H	162.7-164.7	HRMS: Calcd.	469.0392
			HRMS: Found	469.0393

187

Example 123

5 4-[(4-Methylsulfonyl)phenyl]-5-(3,4-dichlorophenyl)oxazole-2-butanoic acid

Step 1: Preparation of 2-(3,4-dichlorophenyl)-2-hydroxy-1-[(4-methylthio)-phenyl]ethanone

10 Trimethylsilyl cyanide (14.6 g, 0.147 mol) was diluted with 30 mL of methylene chloride and added to a solution of 3,4-dichlorobenzaldehyde (25 g, 0.143 mol) in 100 mL of methylene chloride over 20 minutes. The reaction mixture was stirred at room temperature for 1
15 h. The reaction mixture was diluted with 200 mL of methylene chloride, and the organic solution was washed with saturated sodium bicarbonate (2 x 150 mL), saturated brine (2 x 150 mL), dried over magnesium sulfate, filtered and concentrated to give 39 g of a
20 brown oil, which was used in the next reaction without further purification.

 Magnesium (1.8 g, 0.073 mol) was suspended in ether (20 mL), and iodomethane (0.1 mL) was added. 4-Bromothioanisole (14.8 g, 0.073 mol), dissolved in 100
25 mL of ether, was added over 50 min., and the reaction mixture was stirred overnight at room temperature. The cyanohydrin (10 g, 0.036 mol) was diluted with 100 mL of ether and added to the pre-formed Grignard reagent over a 1 h period. The reaction mixture was stirred for 3 h
30 at room temperature. The reaction was slowly quenched

with 50 mL of 3 N HCl and the aqueous layer was removed by separation. The organic layer was washed with water (2 x 100 mL), saturated sodium bicarbonate (1 x 100 mL), saturated brine (1 x 100 mL), dried over magnesium sulfate, filtered and concentrated. A solution of 9:1 trifluoroacetic acid:water (50 mL) was added to the concentrated residue, and the mixture was stirred for 1.5 h at room temperature. The reaction mixture was neutralized by adding solid sodium carbonate. Water (300 mL) and ether (300 mL) were added. The ether layer was separated and washed with saturated sodium bicarbonate (2 x 150 mL), saturated brine (2 x 150 mL), dried over magnesium sulfate, filtered and concentrated. The crude material was purified by flash chromatography on silica gel eluting with 1:9 ethyl acetate:hexane to give 3.3 g (28%) of the desired benzoin as a yellow oil. This yellow oil was crystallized from hexane and ethyl acetate to give 0.46 g of 2-(3,4-dichlorophenyl)-2-hydroxy-1-[(4-methylthio)phenyl]ethanone as a white solid: m.p. 54-58 °C. HRMS (calcd for C₁₅H₁₂O₂SCl₂ 327.0013) 327.0024.

Step 2: Preparation of methyl 4-[(4-methylthio)phenyl]-5-(3,4-dichlorophenyl)oxazole-2-butanoate

5-(Methoxycarbonyl)pentanoyl chloride (1.63 g, 9.9 mmol) was diluted with 20 mL of methylene chloride and was added to a solution of 2-(3,4-dichloro-phenyl)-2-hydroxy-1-[(4-methylthio)phenyl]ethanone (Step 1) (3.24 g, 9.9 mol) in 60 mL of methylene chloride containing triethylamine (2 g, 0.02 mmol). The reaction mixture was stirred for 1.5 h at room temperature. The reaction mixture was diluted with 100 mL of methylene chloride and washed with water (1 x 100 mL), saturated brine (1 x 100 mL), dried over magnesium sulfate, filtered, concentrated and dried under high vacuum. Acetic acid

(10 mL) and ammonium acetate (3.05 g, 0.04 mol) were added to this concentrated residue, and the mixture was heated at 100 °C for 3 h. The reaction mixture was cooled to room temperature, and the excess acetic acid was removed under vacuum. The resulting residue was partitioned between water (100 mL) and ethyl acetate (200 mL). The organic layer was separated, washed with saturated aqueous sodium bicarbonate (2 x 100 mL), saturated brine (1 x 100 mL), dried over magnesium sulfate, filtered and concentrated. The concentrated residue was purified by flash chromatography on silica gel (eluting with 1:4 ethyl acetate:hexane) to give 2.14 g (50%) of methyl 4-[(4-methylthio)phenyl]-5-(3,4-dichlorophenyl)oxazole-2-butanoate as a yellow oil.

Step 3: Preparation of methyl 4-[(4-methylsulfonyl)phenyl]-5-(3,4-dichlorophenyl)oxazole-2-butanoate

Methyl 4-[(4-methylthio)phenyl]-5-(3,4-dichlorophenyl)oxazole-2-butanoate (1.7 g, 3.89 mmol) from Step 2 was dissolved in 60 mL of methanol:water (9:1), then Oxone® (8.38 g, 0.014 mol) was added. The reaction mixture was stirred for 3 h at room temperature, and the solvents were removed under reduced pressure. The resulting residue was partitioned between water (100 mL) and ethyl acetate (200 mL). The organic layer was separated, washed with saturated aqueous sodium bicarbonate (2 x 100 mL), saturated brine (2 x 100 mL), dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography on silica gel (eluting with 3:7 ethyl acetate:hexane) to give 0.6 g (33%) of methyl 4-[(4-methylsulfonyl)phenyl]-5-(3,4-dichlorophenyl)oxazole-2-butanoate as a clear oil: ¹H NMR (CDCl₃/300 MHz) 2.15-2.25 (m, 2H), 2.52 (t, 2H, J = 7.35 Hz), 2.94 (t, 2H, J = 7.35 Hz), 3.09 (s, 3H), 3.70 (s, 3H), 7.36 (dd, 1H, J

190

= 2.01 Hz), 7.46 (d, 1H, J = 8.46 Hz), 7.69 (d, 1H, J = 2.01 Hz), 7.85 (d, 2H, J = 8.66 Hz), 7.96 (d, 2H, J = 8.46 Hz). HRMS (calcd for C₂₁H₁₉NO₅SCl₂ 468.0439) 468.0435.

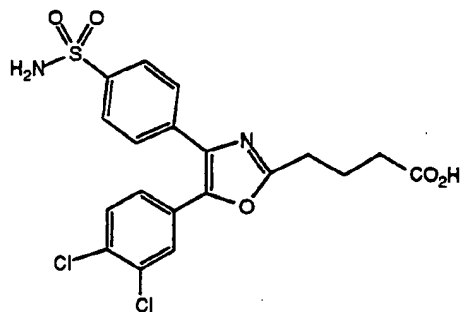
5

Step 4: Preparation of 4-[(4-methylsulfonyl)phenyl]-5-(3,4-dichlorophenyl)oxazole-2-butanoic acid

The methyl ester (0.5 g, 1.07 mmol) from Step 3 was mixed with 15 mL of methanol, lithium hydroxide (0.18 g, 4.27 mmol) and 1 mL of water. The reaction mixture was stirred for 1 h at room temperature and quenched with 15 mL of 1N HCl. The solvents were removed, and the resulting residue was partitioned between 1 N HCl (100 mL) and ethyl acetate (100 mL). The organic layer was separated, washed with 1 N HCl (1 x 100 mL), saturated brine (1 x 100 mL), dried over magnesium sulfate, filtered and concentrated. The concentrated residue was crystallized from methylene chloride and hexane to give 0.26 g (54%) of 4-[(4-methylsulfonyl)phenyl]-5-(3,4-dichlorophenyl)oxazole-2-butanoic acid as white crystals: m.p. 181.7-182.9 °C. ¹H NMR (CD₃OD/300 MHz) 2.10-2.20 (m, 2H), 2.48 (t, 2H, J = 7.15 Hz), 2.97 (t, 2H, J = 7.45 Hz), 3.16 (s, 3H), 7.46 (dd, 1H, J = 2.11 Hz), 7.58 (d, 1H, J = 8.46 Hz), 7.74 (d, 1H, J = 2.01 Hz), 7.85 (d, 2H, J = 8.66 Hz), 8.00 (d, 2H, J = 8.66 Hz). HRMS (calcd for C₂₀H₁₇NO₅SCl₂ 454.0283) 454.0277.

25

Example 124



30

4-[(4-Aminosulfonyl)phenyl]-5-(3,4-dichlorophenyl)oxazole-2-butanoic acid

5 Step 1: Preparation of 2-(3,4-dichlorophenyl)-2-hydroxy-1-phenylethanone

Trimethylsilyl cyanide (14.6 g, 0.147 mol) was dissolved in 30 mL of methylene chloride and added over 20 minutes to a solution of 3,4-dichloro-benzaldehyde
10 (25 g, 0.143 mol) and zinc iodide (0.41 g, 1.28 mmol) in 100 mL of methylene chloride. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with 200 mL of methylene chloride and the organic layer was washed with saturated sodium
15 bicarbonate (2 x 150 mL), saturated brine (2 x 150 mL), dried over magnesium sulfate, filtered and concentrated to give 38.4 g (98%) of a brown oil, which was used in the next reaction without further purification.

This trimethylsilyl cyanohydrin (15 g, 0.0547 mol)
20 was dissolved in 20 mL of diethyl ether and added to phenylmagnesium bromide (19.5 mL of 3.0 M in ether solution, 0.0585 mol) in 250 mL of ether over 15 minutes. The reaction mixture was stirred for 1.5 h at room temperature, then slowly quenched with 100 mL of 3
25 N HCl. The organic layer was separated and washed with saturated sodium bicarbonate (1 x 150 mL), saturated brine (1 x 150 mL), dried over magnesium sulfate, filtered and concentrated to give 13.0 g of a brown oil. A solution of 9:1 trifluoroacetic acid in water (50 mL)
30 was added to the concentrated residue, and the mixture was stirred for 1.5 h at room temperature. The reaction mixture was neutralized by adding solid sodium carbonate. The resulting residue was partitioned between water (200 mL) and ethyl acetate (300 mL). The
35 organic layer was separated, washed with saturated sodium bicarbonate (1 x 150 mL), saturated brine (1 x

192

150 mL), dried over magnesium sulfate, filtered and concentrated. The concentrated residue was crystallized from ethyl acetate and hexane to give 7.37 g (48%) of 2-(3,4-dichlorophenyl)-2-hydroxy-1-(phenyl)ethanone as a yellow solid: HRMS (calcd. for $C_{14}H_{10}O_2Cl_2$ 281.0136) 281.0112.

Step 2: Preparation of methyl [(4-phenyl)-5-(3,4-dichlorophenyl)oxazole]-2-butanoate

10 5-(Methoxycarbonyl)pentanoyl chloride (2.82 g, 0.017 mol) and triethylamine (3.47 g, 0.034 mol) were added to a solution of 2-(3,4-dichlorophenyl)-2-hydroxy-1-[phenyl]ethanone (Step 1) (4.77 g, 0.017 mmol) in 40 mL of methylene chloride. The resulting mixture was stirred overnight at room temperature. The reaction mixture was diluted with 100 mL of methylene chloride. The organic solution was washed with water (1 x 100 mL), saturated brine (1 x 100 mL), dried over magnesium sulfate, filtered, concentrated and dried under high vacuum. Ammonium acetate (4.6 g, 0.06 mol) and 30 mL of acetic acid were added. The reaction mixture was heated at 100 °C for 2.5 h. The reaction mixture was cooled to room temperature, and the excess acetic acid was removed under vacuum. The resulting residue was partitioned between water (100 mL) and ethyl acetate (200 mL). The organic layer was separated, washed with saturated aqueous sodium bicarbonate (2 x 100 mL), saturated brine (1 x 100 mL), dried over magnesium sulfate, filtered and concentrated. The concentrated residue was purified by flash chromatography on silica gel (eluting with 1:9 ethyl acetate:hexane) to give 2.82 g (42.6%) of methyl [(4-phenyl)-5-(3,4-dichlorophenyl)oxazole]-2-butanoate as a yellow oil: HRMS (calcd. for $C_{20}H_{17}NO_3Cl_2$ 390.0664) 390.0648.

35

Step 3: Preparation of methyl 4-[(4-aminosulfonyl)phenyl]-5-(3,4-dichlorophenyl)oxazole-2-butanoate

Chlorosulfonic acid (28 g, 0.24 mol) was added to methyl [(4-phenyl)-5-(3,4-dichlorophenyl)oxazole]-2-butanoate (Step 2) (3.74 g, 9.58 mmol) at 5 °C. The ice bath was removed, and the reaction was stirred for 3 h at room temperature. The reaction mixture was diluted with 100 mL of methylene chloride and slowly poured into ice. The organic layer was separated and washed with saturated brine (1 x 100 mL). The organic layer was separated, poured into 50 mL of concentrated ammonium hydroxide and stirred for 30 minutes at room temperature. The organic layer was separated, washed with water (1 x 100 mL), saturated brine (1 x 100 mL), dried over magnesium sulfate, filtered and concentrated. The crude material was crystallized from methanol and water to give 1.7 g (38%) of methyl 4-[(4-aminosulfonyl)phenyl]-5-(3,4-dichlorophenyl)oxazole-2-butanoate as a yellow solid: m.p. 130.7-131.8 °C. HRMS (calcd. for C₂₀H₁₈N₂O₅Cl₂ 469.0392) 469.0413.

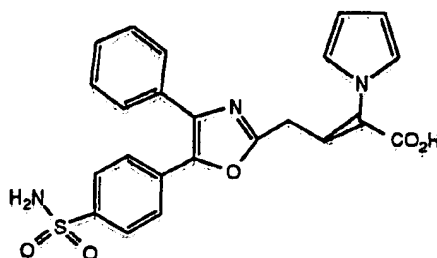
Step 4: Preparation of 4-[(4-aminosulfonyl)phenyl]-5-(3,4-dichlorophenyl)oxazole-2-butanolic acid

Methyl 4-[(4-aminosulfonyl)phenyl]-5-(3,4-dichlorophenyl)oxazole-2-butanoate (Step 3) (0.6 g, 1.28 mmol) was dissolved in 30 mL of 1:1 methanol/THF. Lithium hydroxide (0.21 g, 5.11 mmol) and 3 mL of water were added. The reaction mixture was stirred for 18 h at room temperature. The solvents were removed, and the resulting residue was partitioned between 1 N HCl (100 mL) and ethyl acetate (100 mL). The organic layer was separated and washed with saturated sodium bicarbonate (1 x 100 mL). The aqueous layer was acidified by adding excess 3N HCl and extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with

194

saturated brine (1 x 100 mL), dried over magnesium sulfate, filtered and concentrated to give 0.27 g (46%) of 4-[(4-aminosulfonyl)phenyl]-5-(3,4-dichlorophenyl)-oxazole-2-butanoic acid as a yellow solid: m.p. 168-171 °C. HRMS (calcd for C₁₉H₁₆N₂O₅SCl₂ 455.0235) 455.0197.

Example 125



5-[4-[(Aminosulfonyl)phenyl]-4-phenyl-αS-(1H-pyrrol-1-yl)oxazole-2-butanoic acid

Step 1: Preparation of methyl 5-[4-aminosulfonyl)phenyl]-αS-[(phenylmethoxy)carbonyl]aminol-4-phenyloxazole-2-butanoate

A solution of 2-bromo-2-[(4-aminosulfonyl)phenyl]-1-phenylethanone (1.0 g, 2.8 mmol) and N-Cbz-glutamic acid α-methyl ester (0.92 g, 3.1 mmol) in dimethylacetamide (5.0 mL) was treated with K₂CO₃ (0.27 g, 1.96 mmol) and 18-crown-6 (0.05 g), and stirred at room temperature for 3.5 h. The reaction mixture was poured into water (50 mL) and extracted with EtOAc (3 x 25 mL). The combined organic phase was washed with water (2 x 25 mL), dried (Na₂SO₄), filtered, and concentrated to give an amorphous pale yellow substance. This material was dried in vacuo for 3 h, then dissolved in glacial acetic acid (10 mL). After adding NH₄OAc (0.7 g, 9.1 mmol), the resulting mixture was heated at 100 °C for 2.5 h under a nitrogen atmosphere. The acetic acid

195

was removed in vacuo, and the residue was partitioned between water (50 mL) and EtOAc (50 mL). The organic phase was washed with water, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (eluting with 40% EtOAc in hexane) to give 0.9 g (58%) of methyl 5-[(4-aminosulfonyl)phenyl]- α S-[[(phenylmethoxy)carbonyl]amino]-4-phenyloxazole-2-butanoate as a white amorphous substance: $^1\text{H-NMR}$ ($\text{CD}_3\text{OD}/300\text{ MHz}$) 7.86 (d, 2H, $J = 8.4\text{ Hz}$), 7.66 (d, 2H, $J = 8.4\text{ Hz}$), 7.54 (m, 2H), 7.4 (m, 3H), 7.3 (s, 5H), 5.05 (s, 2H), 4.4 (m, 1H), 3.72 (s, 3H), 3.01 (t, 2H, $J = 7.2\text{ Hz}$), 2.42 (m 1H), 2.21 (m, 1H); FABMS: $m/z = 550\text{ (M+H}^+)$ HRMS (calcd for $\text{C}_{28}\text{H}_{28}\text{N}_3\text{O}_7\text{S}$ 550.1648) 550.1616.

Step 2: Preparation of methyl 5-[4-(aminosulfonyl)phenyl]-4-phenyl- α S-(1H-pyrrol-1-yl)oxazole-2-butanoate

A solution of methyl 5-[(4-aminosulfonyl)phenyl]- α S-[[(phenylmethoxy)carbonyl]amino]-4-phenyloxazole-2-butanoate (Step 1) (1.0 g, 1.82 mmol) in EtOAc (20 mL) was treated with 10% Pd/C (0.5 g) and hydrogenated at 50 psi for 3 h at room temperature. The catalyst was removed by filtration, and the filtrate was concentrated. The residue was dissolved in glacial acetic acid (10 mL), then NaOAc (0.9 g) and 2,5-dimethoxytetrahydrofuran (0.26 g, 2.0 mmol) were added, and the mixture was heated at 100 °C for 15 min under a nitrogen atmosphere. The acetic acid was removed in vacuo, and the residue was partitioned between water (25 mL) and EtOAc (30 mL). The organic phase was washed with water, dried (Na_2SO_4), filtered, and concentrated. The resulting material was purified by silica gel flash chromatography eluting with 45% EtOAc in hexane, to give 0.35 g (41%) of methyl 5-[4-(aminosulfonyl)phenyl]-4-phenyl- α S-(1H-pyrrol-1-yl)oxazole-2-butanoate as a white amorphous material: $^1\text{H-NMR}$ ($\text{CD}_3\text{OD}/300\text{ MHz}$)

196

7.87 (d, 2H, J = 8.7 Hz), 7.66 (d, 2H, J = 8.7 Hz),
7.54 (m, 2H), 7.42 (m, 3H), 6.79 (t, 2H, J = 2.1 Hz),
6.09 (t, 2H, J = 2.1 Hz), 4.95 (m, 1H), 3.72 (s, 3H),
2.86-2.45 (m, 4H) FABMS m/z = 466 (M+H⁺). HRMS (calcd
5 for C₂₄H₂₄N₃O₅S 466.1437) 466.1458.

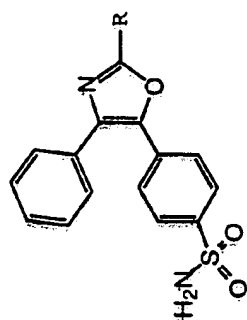
Step 3: Preparation of 5-[4-[(Aminosulfonyl)phenyl]-4-phenyl- α S-(1H-pyrrol-1-yl)oxazole-2-butanoic acid

A solution of methyl 5-[4-(aminosulfonyl)
10 phenyl]-4-phenyl- α S-(1H-pyrrol-1-yl)oxazol-2-butanoate
(Step 2) (0.2 g, 0.43 mmol) in MeOH (0.3 mL) and water
(0.3 mL) was treated with NaOH (0.026 g) and stirred at
room temperature for 1.5 h. The reaction mixture was
diluted with 5% citric acid (10 mL) and extracted with
15 EtOAc (2 x 20 mL). The combined organic extracts were
washed with water, dried (Na₂SO₄), filtered, and
concentrated under reduced pressure. The resulting
substance was purified by reverse-phase HPLC (using 10-
90% CH₃CN in water (30 min gradient)). The appropriate
20 fractions were combined and freeze-dried to give 0.15 g
(78%) of 5-[4-[(aminosulfonyl)phenyl]-4-phenyl- α S-(1H-
pyrrol-1-yl)oxazole-2-butanoic acid as a light brown
powder: m.p. 74-78 °C. ¹H-NMR (CD₃OD/300 MHz) 7.87 (d,
2H, J = 8.7 Hz), 7.66 (d, 2H, J = 8.7 Hz), 7.55 (m, 2H),
25 7.44 (m, 3H), 6.79 (t, 2H, J = 2.1 Hz), 6.08 (t, 2H, J =
2.1 Hz), 4.91 (m, 1H), 2.85-2.45 (m, 4H) FABMS m/z = 452
(M+H⁺) HRMS (calcd for C₂₃H₂₂N₃O₅S 452.1280) 452.1291.

Other representative examples prepared by similar
methods are summarized in Table 3.

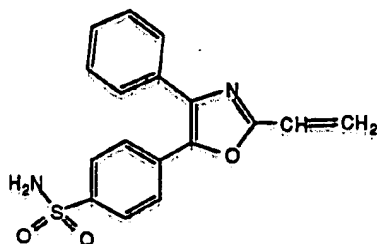
30

TABLE 3



Example No.	R	m.p. (°C)	Analyses	
126		48-63	HRMS: Calcd. 407.1304 HRMS: Found 407.1286	
127		75-84	HRMS: Calcd. 393.1147 HRMS: Found 393.1152	
128		53-59	HRMS: Calcd. 393.1147 HRMS: Found 393.1152	

198

Example 129

5 **4-(2-Ethenyl-4-phenyloxazol-5-yl)benzenesulfonamide**

10 Step 1: Preparation of 2-[5-[(4-aminosulfonyl)phenyl]-4-phenyl-oxazol-2-yl]-1-hydroxyethane

Lithium aluminum hydride (0.33 g, 8.6 mmol) was suspended in 5 mL of anhydrous THF and cooled to -78 °C. Methyl 5-[(4-aminosulfonyl)phenyl]-4-phenyloxazole-2-acetate (1.6 g, 4.3 mmol) (prepared similar to that described in Example 38, step 3) was dissolved in 15 mL of anhydrous THF and added at -78 °C. The reaction mixture was stirred at -78 °C for 2 h, stirred at room temperature overnight, and quenched with 50 mL of 1 N HCl. The aqueous solution was extracted with ethyl acetate (2 x 100 mL). The combined organic extracts were washed with saturated sodium bicarbonate (1 x 100 mL), saturated brine (1 x 100 mL), dried over magnesium sulfate, filtered and concentrated. The concentrated residue was purified by flash chromatography on silica gel (eluting with 3:2 ethyl acetate:hexane to 4:1 ethyl acetate:hexane) to give 0.2 g (14%) of 2-[5-[(4-aminosulfonyl)phenyl]-4-phenyl-oxazol-2-yl]-1-hydroxyethane as a white solid: ¹H NMR (DMSO-d₆/300 MHz) 2.98 (t, 2H, J = 6.45 Hz), 3.81-3.87 (m, 2H), 4.91 (t, 1H, J = 5.4 Hz), 7.35-7.46 (m, 5H), 7.56

199

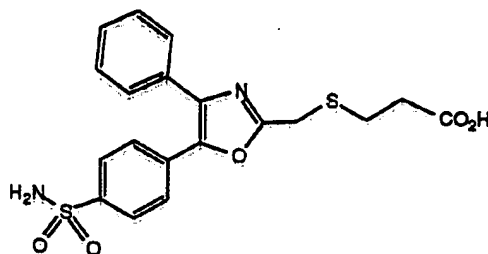
(dd, 2H, $J = 1.65$ Hz), 7.68 (d, 2H, $J = 8.7$ Hz),
7.84 (d, 2H, $J = 8.7$ Hz). HRMS (calcd for
 $C_{17}H_{16}N_2O_4S$ 345.0909) 345.0902.

5 Step 2: Preparation of 4-(2-ethenyl-4-
phenyloxazol-5-yl)benzenesulfonamide

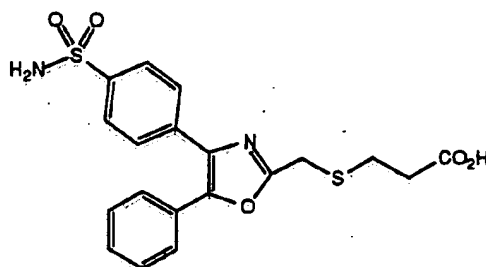
2-[5-[(4-aminosulfonyl)phenyl]-4-phenyl-oxazol-
2-yl]-1-hydroxyethane (Step 1) (0.2 g, 0.58 mmol) in
4 mL of dimethylacetamide (DMA) was added to NaH
10 suspended in 1 mL of DMA at 5 °C. The reaction
mixture was stirred at 5 °C for 30 minutes. 4-[4-
Bromomethylphenyl]-4-methoxytetrahydropyran (0.2 g,
0.70 mmol) was dissolved in 3 mL of DMA and added to
the reaction at 5 °C. The reaction mixture was
15 stirred at 5 °C for 1.5 h and at room temperature
overnight. The DMA was removed at reduced pressure,
and the concentrated residue was dissolved in 150 mL
of ethyl acetate. The organic solution was washed
with 1 N HCl (2 x 100 mL), saturated sodium
20 bicarbonate (2 x 100 mL), saturated brine (2 x 100
mL), dried over magnesium sulfate, filtered and
concentrated. The concentrated residue was filtered
through silica gel (eluting with 4:1 ethyl
acetate:hexane). The material recovered from this
25 column was purified by reverse phase HPLC (eluting
with a gradient from 10% to 90% acetonitrile in
water with 0.1% TFA) to give 15 mg (8%) of 4-(2-
ethenyl-4-phenyloxazol-5-yl)benzenesulfonamide as a
white solid: 1H NMR($CD_3OD/300$ MHz) 5.82 (d, 1 H, J
30 = 11.70 Hz), 6.38 (d, 1H, $J = 17.40$ Hz), 6.71 (dd,
1H, $J = 11.10$ Hz), 7.43-7.45 (m, 3H), 7.57-7.60 (m,
2H), 7.74 (d, 2H, $J = 8.70$ Hz), 7.89 (d, 2H, $J =$
8.40 Hz). HRMS (calcd for $C_{17}H_{14}N_2O_3S$ 327.0803)
327.0800.

35

200

Example 130

5 3-[[[5-[4-Aminosulfonyl]phenyl]-4-phenyloxazol-2-yl]methyl]thiolpropanoic acid

Example 131

10

3-[[[4-[4-Aminosulfonyl]phenyl]-5-phenyloxazol-2-yl]methyl]thiolpropanoic acid

15 Step 1: Preparation of tert-butyl 3-[(2-methoxy-2-oxoethyl)thiol]propanoate

 A solution of tert-butyl acrylate (3.7 g, 0.03 mol) and methyl thioglycolate (3.3 g, 0.31 mol) in CH₂Cl₂ (10 mL) was treated with DBU (0.3 g, 0.002 mol), and stirred at 10 °C for 2 h. The reaction mixture was diluted with CH₂Cl₂ (100 mL), washed sequentially with 5% citric acid (2 x 50 mL), brine (2 x 50 mL), and dried (Na₂SO₄). After the removal of the solvent, the resulting liquid was purified by silica gel flash chromatography (eluting with 30% EtOAc in hexane) to give 6.0 g (90%) of tert-butyl

201

3-[(2-methoxy-2-oxoethyl)-thio]propanoate as a colorless liquid: $^1\text{H-NMR}$ ($\text{CDCl}_3/300\text{ MHz}$) 3.75 (s, 3H), 3.26 (s, 2H), 2.87 (t, 2H, $J = 6.9\text{ Hz}$), 2.55 (t, 2H, $J = 6.9\text{ Hz}$), 1.46 (s, 9H).

5

Step 2: Preparation of tert-butyl 3-[(carboxymethyl)thio]propanoate

A solution of tert-butyl 3-[(2-methoxy-2-oxoethyl)thio]propanoate (Step 1) (2.0 g, 8.5 mmol) in MeOH (6.00 mL) and water (4.0 mL) was treated with LiOH (0.45 g, 10.8 mmol) and stirred at room temperature for 2 h. The reaction mixture was diluted with water (15 mL) and washed with EtOAc (2 x 10 mL). The aqueous phase was acidified with 5% citric acid and extracted with EtOAc (2 x 15 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated to give 1.1 g (59%) of tert-butyl 3-[(carboxymethyl)thio]propanoate as a colorless liquid which was used in the next step without further purification: $^1\text{H-NMR}$ ($\text{CDCl}_3/300\text{ MHz}$) 3.31 (s, 2H), 2.85 (t, 2H, $J = 6.9\text{ Hz}$), 2.58 (t, 2H, $J = 6.9\text{ Hz}$), 1.47 (s, 9H).

25

Step 3: Preparation of tert-butyl 3-[[[5-[4-aminosulfonyl]phenyl]-4-phenyl-oxazol-2-yl]methyl]-thio]propanoate and tert-butyl 3-[[[4-[4-aminosulfonyl]-phenyl]-5-phenyloxazol-2-yl]methyl]thio]propanoate

30

A mixture of 2-bromo-2-[(4-aminosulfonyl)phenyl]-1-phenylethanone (1.3 g, 3.7 mmol), tert-butyl 3-[(carboxymethyl)thio]propanoate (Step 2) (1.0 g, 4.5 mmol), and K_2CO_3 (0.40 g, 2.9 mmol) in dimethylacetamide (5.0 mL) was stirred at 10 °C for 2 h, and at room temperature for 1 h. The

35

reaction mixture was diluted with water (50 mL), and extracted with EtOAc (2 x 25 mL). The combined organic extracts were washed with water (2 x 25 mL), dried (Na₂SO₄), filtered, and concentrated to give the desired α -acyloxy ketone. The resulting viscous liquid (1.5 g) was used in the following reaction without further purification.

This α -acyloxy ketone (1.3 g) was dissolved in acetic acid (20 mL), NH₄OAc (0.8 g, 10.4 mmol) was added, and the resulting mixture was heated at 100 °C for 2.5 h under a nitrogen atmosphere. The acetic acid was distilled *in vacuo*, and the residue was partitioned between water (25 mL) and EtOAc (30 mL). The organic phase was washed with water, dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel flash chromatography (eluting with 40% EtOAc in hexane) to give 0.45 g (36%) of a mixture of tert-butyl 3-[[[5-[4-aminosulfonyl]phenyl]-4-phenyl-oxazol-2-yl]methyl]thiol]propanoate and tert-butyl 3-[[[4-[4-amino-sulfonyl]phenyl]-5-phenyloxazol-2-yl]methyl]-thiol]propanoate oxazole esters, as a light brown amorphous substance: m.p. 49-54 °C. ¹H-NMR (CDCl₃/300 MHz) 7.81 (d, 2H, J = 7.8 Hz), 7.66 (d, 2H, J = 7.8 Hz), 7.52 (m, 2H), 7.33 (m, 3H), 4.84 (s, 2H), 3.83 (s, 2H), 2.87 (t, 2H, J = 6.9 Hz), 2.53 (t, 2H, J = 6.9 Hz), 1.37 (s, 9H). HRMS (calcd for C₂₃H₂₇N₂O₅S₂ 475.1361) 475.1326.

Step 4: Preparation of 3-[[[5-[4-aminosulfonyl]phenyl]-4-phenyloxazol-2-yl]methyl]-thiol]propanoic acid and 3-[[[4-[4-aminosulfonyl]phenyl]-5-phenyloxazol-2-yl]methyl]thiol]propanoic acid

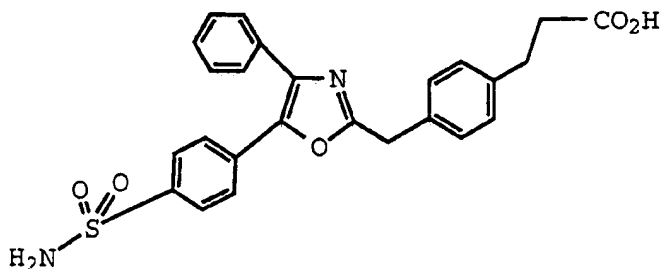
A mixture of the oxazole esters (0.25 g, 5.2 mmol) Step 3, and p-toluenesulfonic acid (0.06 g 0.3

mmol) in acetonitrile (5.0 mL) was heated to reflux for 1.5 h under a nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure, and the residue was partitioned between water (10 mL) and EtOAc (20 mL). The organic phase was washed with water, dried (Na₂SO₄), filtered, concentrated, and the resulting substance was purified by reverse-phase HPLC (10-90% CH₃CN/H₂O) to give two isomeric products: 3-[[[5-[4-aminosulfonyl]phenyl]-4-phenyloxazol-2-yl]methyl]thio]propionic acid as a white powder; (0.16 g (73%)) m.p. 170-173 °C ¹H-NMR (CD₃OD/300 MHz) 7.9 (d, 2H, J = 8.7 Hz), 7.71 (d, 2H, J = 8.7 Hz), 7.57 (m, 2H), 7.42 (m, 3H), 3.98 (s, 2H), 2.95 (t, 2H, J = 7.2 Hz), 2.67 (t, 2H, J = 7.2 Hz); HRMS (calcd for C₁₉H₁₉N₂O₅S₂ 419.0735) found 419.0700;

3-[[[4-[4-aminosulfonyl]phenyl]-5-phenyl-oxazol-2-yl]methyl]thio]propionic acid as a light brown powder: (0.03 g (14%)) m.p. 171-175 °C; ¹H-NMR (CD₃OD/300 MHz) 7.91 (d, 2H, J = 8.4 Hz), 7.76 (d, 2H, J = 8.4 Hz), 7.56 (m, 2H), 7.43 (m, 3H), 3.97 (s, 2H), 2.94 (t, 2H, J = 6.9 Hz), 2.67 (t, 2H, J = 6.9 Hz); HRMS (calcd for C₁₉H₁₉N₂O₅S₂ 419.0735) 419.0708.

25

Example 132



30

4-[[[5-[(4-Aminosulfonyl)phenyl]-4-phenyl-oxazol-2-yl]methyl]benzenepropanoic acid

Step 1: Preparation of 5-[(4-aminosulfonyl)phenyl]-4-phenyl-2-[(4-iodophenyl)methyl]oxazole

5 A mixture of 2-bromo-2-[(4-aminosulfonyl)phenyl]-1-phenylethanone (2.0 g, 5.65 mmol) and 4-iodophenylacetic acid (1.8 g, 6.9 mmol) in dimethylacetamide (6.0 mL) was treated with potassium carbonate (0.57 g, 4.13 mmol) and 18-crown-6 (0.06 g) and stirred at room temperature for 4 h. The reaction mixture was diluted with cold water (50 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic phases were washed with water (2 x 25 mL), dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The resulting material was purified by flash chromatography on silica gel (eluting with 40% EtOAc in hexane) to give the desired α -acyloxy ketone as an amorphous substance, which was used in the next reaction without further purification: ¹H-NMR (CDCl₃/300 MHz) 7.86 (m, 4H), 7.63 (d, 2H, J = 8.4 Hz), 7.59 (m, 3H), 7.41 (t, 2H, J = 7.8 Hz), 7.03 (d, 2H, J = 8.4 Hz), 6.89 (s, 1H), 4.82 (s, 2H), 3.73 (q, 2H, J = 5.1 Hz). FABMS m/z = 536 (M+H⁺). HRMS (calcd for C₂₂H₁₉NO₅SI 536.0029) 536.0023.

25 A mixture of this α -acyloxy ketone (2.2 g, 4.1 mmol), and ammonium acetate (1.3 g, 16.9 mmol) in acetic acid (15.0 mL) was heated at 100 °C under a nitrogen atmosphere for 2.5 h. The reaction mixture was concentrated in vacuo, and the residue was partitioned between water (50 mL) and EtOAc (50 mL). The organic phase was washed with water (2 x 30 mL), dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The resulting solid was triturated with methanol, cooled and filtered to

give 1.1 g (52%) of 5-[(4-aminosulfonyl)phenyl]-4-phenyl-2-[(4-iodophenyl)methyl]oxazole as a pale yellow powder: m.p. 198-201 °C. ¹H-NMR (CDCl₃/ 300 MHz) 7.86 (d, 2H, J = 8.7 Hz), 7.7 (dd, 4H), 7.59 (m, 2H), 7.41 (m, 3H), 7.15 (d, 2H, J = 8.1 Hz), 4.81 (s, 2H), 4.16 (s, 2H). FABMS m/z = 517 (M+H⁺) HRMS (calcd for C₂₂H₁₈N₂O₃SI 517.0083) 517.0063.

10 Step 2: Preparation of methyl 4-[[5-[(4-aminosulfonyl)phenyl]-4-phenyl-oxazol-2-yl]methyl]benzenepropynoate

To a solution of 5-[(4-aminosulfonyl)phenyl]-4-phenyl-2-[(4-iodophenyl)methyl]oxazole (Step 1) (0.3 g, 0.58 mmol) in dimethylacetamide (5.00 mL) was added K₂CO₃ (0.05 g, 0.3 mmol), 18-crown-6 (0.05 g), PdCl₂·(PPh₃)₂, methyl propiolate (0.32 g, 3.8 mmol) and CuI (0.005 g), and the resulting mixture was stirred at room temperature for 16 h under an argon atmosphere. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (2 x 25 mL). The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated under reduced pressure. This residue was purified by silica gel flash chromatography (25% EtOAc in hexane) to afford 0.11 g (40%) of methyl 4-[[5-[(4-amino-sulfonyl)phenyl]-4-phenyl-oxazol-2-yl]methyl]benzenepropynoate as a brown amorphous powder: ¹H-NMR (CDCl₃/300 MHz) 7.87 (d, 2H, J = 8.7 Hz), 7.68 (d, 2H, J = 8.7 Hz), 7.59 (m, 4H), 7.43 (m, 5H), 4.78 (s, 2H), 4.25 (s, 2H), 3.84 (s, 3H) FABMS m/z = 473 (M+H⁺) HRMS (calcd for C₂₆H₂₁N₂O₅S 473.1171) 473.1181.

35 Step 3: Preparation of 4-[[5-[(4-aminosulfonyl)phenyl]

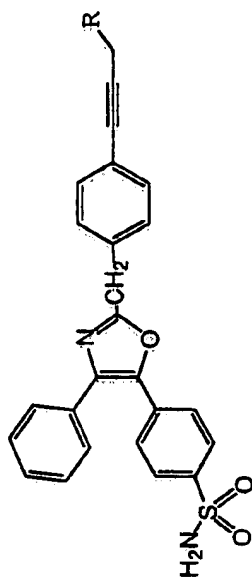
-4-phenyl-oxazol-2-yl)methyl]benzenepropanoic acid

A mixture of methyl 4-[[5-[(4-aminosulfonyl)phenyl]-4-phenyl-oxazol-2-yl)methyl]benzenepropynoate (Step 5 2) (0.12 g, 0.25 mmol) in MeOH (5 mL) was hydrogenated in the presence of 10% Pd/C (0.13 g) at 50 psi for 3 h at room temperature. The catalyst was removed by filtration, the filtrate was concentrated, and the residue was stirred with 1M LiOH (1 mL) in MeOH (0.7 mL) and water (0.3 mL) for 10 1 h. The reaction mixture was diluted with 5% citric acid (10 mL) and extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with water, dried (Na₂SO₄), filtered, and concentrated under reduced pressure to afford 0.08 g (69%) of 4-[[5-[(4-aminosulfonyl)phenyl]-4-phenyl-oxazol-2-yl)methyl]benzenepropanoic acid as a light brown amorphous powder: ¹H-NMR (CDCl₃/300 MHz) 7.83 (d, 2H, J = 8.7 Hz), 7.66 (d, 2H, J = 8.7 Hz), 7.58 (m, 2H), 7.39 (m, 3H), 7.31 (d, 2H, J = 8.1 Hz), 7.19 (d, 2H, J = 8.1 Hz), 4.9 (s, 2H), 4.18 (s, 2H), 2.95 (t, 2H, J = 7.0 Hz), 2.68 (t, 2H, J = 7.0 Hz) FABMS m/z = 463 (M+H⁺). HRMS (calcd for C₂₅H₂₃N₂O₅S 463.1328) 463.1324.

25

Other representative examples prepared by similar methods from 5-[(4-aminosulfonyl)phenyl]-4-phenyl-2-[(4-iodophenyl)methyl]oxazole are 30 summarized in Tables 3 and 4.

TABLE 4



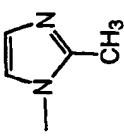
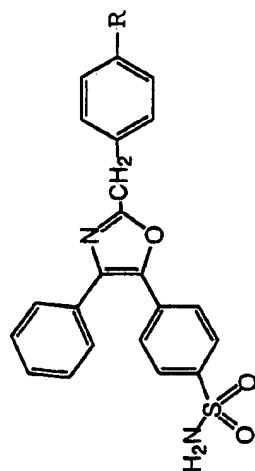
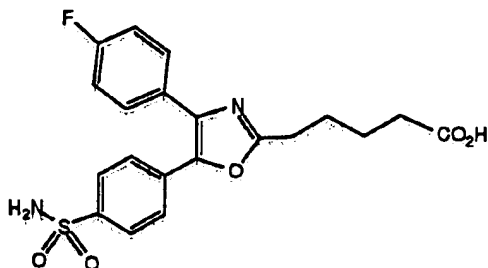
Example No.	R	m.p. (°C)	Analyses
133	-OH	86-94	HRMS: Calcd. 445.1222 HRMS: Found 445.1184
134	-NH ₂ · HCl	>200	HRMS: Calcd. 444.1382 HRMS: Found 444.1358
135	-NHCO ₂ C(CH ₃) ₃	168-170	HRMS: Calcd. 544.1906 HRMS: Found 544.1905
136	-N(CH ₃) ₂	87-91	HRMS: Calcd. 472.1695 HRMS: Found 472.1710
137	-NHC(CH ₃) ₃	>211	HRMS: Calcd. 500.2008 HRMS: Found 500.2008
138		203-204	HRMS: Calcd. 509.1647 HRMS: Found 509.1703

TABLE 5



Example No.	R	m.p. (°C)	Analyses
139	$-(\text{CH}_2)_3\text{N}(\text{CH}_3)_2$	ND	HRMS: Calcd. 476.2008 HRMS: Found 476.2009
140	$-(\text{CH}_2)_4\text{N}(\text{CH}_3)_2$. HCl	ND	HRMS: Calcd. 527.2117 HRMS: Found 527.2126

Example 141

5 **5-[(4-Aminosulfonyl)phenyl]-4-(4-
fluorophenyl)oxazole-2-pentanoic acid**

Step 1. Preparation of 2-[(4-aminosulfonyl)phenyl]-1-(p-
fluorophenyl)-ethanone.

10 Neat 2-(phenyl)-1-(p-fluorophenyl)ethanone (6.10 g,
28.54 mmol) was cooled to -78 °C in a dry ice methanol
bath. Chlorosulfonic acid (15.0 mL) was added, and the
solution was warmed to room temperature over 1 h. The
solution was stirred for 2 h and poured directly into
15 ice. The resulting heterogenous aqueous solution was
extracted with ethyl acetate (2 x 300 mL). The ethyl
acetate layers were combined, extracted with water (1 x
100 mL) and mixed with ammonium hydroxide solution (50
mL) for 1 h. The ethyl acetate was collected, extracted
20 with 1N HCl (2 x 200 mL), brine (1 x 200 mL), and dried
over sodium sulfate. The solvent was removed to a volume
of 50 mL and crystals formed. The crystals were kept at
room temperature for 4 h and collected by vacuum
filtration to give 3.1 g (37%) of 2-[(4-
25 aminosulfonyl)phenyl]-1-(p-fluorophenyl)ethanone: m.p.
198-204 °C. ¹H NMR (CD₃OD/300 MHz) 4.46 (s, 2H), 7.23 (t,
2H, J = 8.8 Hz), 7.43 (d, 2H, J = 8.5 Hz), 7.85 (d, 2H, J
= 8.5 Hz). 8.10-8.20 (m, 2H). FABMS m/z = 294 (m+H⁺) HRMS
(calcd for C₁₄H₁₃FO₃S 294.0600) 294.0583.

Step 2: Preparation of 2-[(4-aminosulfonyl)phenyl]-2-bromo-1-(p-fluoro-phenyl)ethanone

To a solution of 2-[(4-aminosulfonyl)phenyl]-1-(p-fluorophenyl)ethanone (Step 1) (2.93 g, 10.00 mmol) in
5 acetic acid (25 mL) at room temperature was added 33% HBr in acetic acid (5.0 mL), followed by bromine (1.59 g, 10.00 mmol), and the solution was stirred at room
temperature for 1 h. The acetic acid was removed at
reduced pressure, and the resulting yellow liquid was
10 poured into ethyl acetate (100 mL). This solution was washed with saturated sodium bicarbonate (2 x 100 mL), and brine (100 mL). The ethyl acetate layer was dried over anhydrous sodium sulfate, filtered, and the solvent was removed at reduced pressure to give 3.21 g (86%) of
15 2-[(4-aminosulfonyl)phenyl]-2-bromo-1-(p-fluorophenyl)ethanone as a gummy foam: ¹H NMR (CDCl₃/300 MHz) 5.05 (bs, 2H), 6.30 (s, 1H), 7.16 (t, 2H, J = 8.6 Hz), 7.67 (d, 2H, J = 8.5 Hz), 7.92 (d, 2H, J = 8.5 Hz), 8.02-8.07 (m, 2H). FABMS m/z = 389 (m+NH₃⁺). HRMS (calcd for C₁₄H₁₂BrFNO₃S 371.9705) 371.9721.
20

Step 3: Preparation of methyl 5-[(4-aminosulfonyl)phenyl]-4-(4-fluoro-phenyl)oxazole-2-pentanoate

25 A mixture of 2-[(4-aminosulfonyl)phenyl]-2-bromo-1-(p-fluorophenyl)ethanone (Step 2) (760 mg, 2.56 mmol) and the sodium salt of adipic acid monomethyl ester (550 mg, 2.91 mmol) were combined in dimethylformamide (5.0 mL) and stirred at room temperature for 1 h. The solvent was
30 removed at reduced pressure, and the residue was taken up in ethyl acetate (35 mL). This solution was washed with saturated aqueous ammonium chloride (2 x 25 mL), dried over anhydrous sodium sulfate, and the solvent removed at reduced pressure to give 924 mg (80%) of the desired α-
35 acyloxy ketone intermediate as a thick yellow oil: ¹H NMR (CDCl₃/300 MHz) 1.70-1.95 (m, 4H), 2.31 (t, 2H, J = 6.9

211

Hz), 2.43-2.57 (m, 2H), 4.95 (bs, 2H), 6.85 (s, 1H), 7.11 (t, 2H, J = 8.6 Hz), 7.60 (d, 2H, J = 8.3 Hz), 7.91 (d, 2H, J = 8.3 Hz), 7.95-8.00 (m, 2H). FABMS m/z = 452 (m+H⁺). HRMS (calcd for C₂₁H₂₃FNO₇S 452.1179) 452.1209.

5 This α -acyloxy ketone intermediate (861 mg, 1.90 mmol) and ammonium acetate (1014 mg, 13.1 mmol) were refluxed in acetic acid (5 mL) for 2 h. The solution was poured into water (25 mL) and extracted with ethyl acetate (3 x 25 mL). The ethyl acetate extracts were
10 combined and washed with saturated sodium bicarbonate (3 x 50 mL), and saturated aqueous sodium chloride (1 x 50 mL). The solution was dried over anhydrous sodium sulfate, filtered, and the solvent was removed at reduced pressure. The resulting residue was purified by flash
15 chromatography on silica gel to give 371 mg (45%) of methyl 5-[(4-amino-sulfonyl)phenyl]-4-(4-fluorophenyl)-oxazole-2-pentanoate as a gummy yellow semi-solid: ¹H NMR (CD₃OD/300 Mhz) 1.64-1.99 (m, 4H), 2.41 (t, 2H, J = 7.2 Hz), 2.91 (t, 2H, J = 7.3 Hz), 3.65 (s, 3H), 7.17 (t, 2H, J = 8.9 Hz), 7.57-7.61 (m, 2H), 7.67 (d, 2H, J = 8.6 Hz),
20 7.88 (d, 2H, J = 8.6 Hz). FABMS m/z = 433 (m+H⁺). HRMS (calcd for C₂₁H₂₂FN₂O₅S 433.1233) 433.1213.

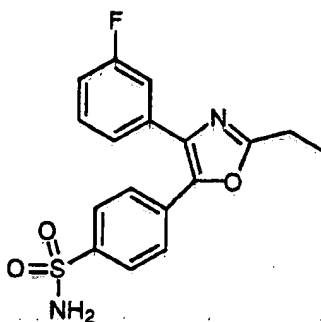
25 Step 4: Preparation of 5-[(4-aminosulfonyl)phenyl]-4-(4-fluorophenyl)-oxazole-2-pentanoic acid

Methyl 5-[(4-aminosulfonyl)phenyl]-4-(4-fluorophenyl)oxazole-2-pentanoate (Step 3) (264.0 mg, 0.61 mmol) and lithium hydroxide monohydrate (100.0 mg, 2.40 mmol) were mixed in tetrahydrofuran/methanol/water
30 (10.0 mL, 7:2:1) at room temperature for 16 h. The solution was acidified with 10% aqueous hydrochloric acid (pH = 1) and poured into ethyl acetate (30 mL). The solution was extracted with 10% aqueous hydrochloric acid (10 mL). The ethyl acetate layer was dried over sodium
35 sulfate, filtered, and the solvent was removed at reduced pressure to give 251 mg (99%) of the desired product 5-

212

[(4-aminosulfonyl)-phenyl]-4-(4-fluorophenyl)-oxazole-2-pentanoic acid as a white solid: m.p. 164.0-165.6 °C. ¹H NMR (CD₃OD/300 MHz) 1.69-1.99 (m, 4H), 2.38 (t, 2H, J = 7.2 Hz), 2.92 (t, 2H, J = 7.3 Hz), 7.17 (t, 2H, J = 8.8 Hz), 7.57-7.61 (m, 2H), 7.68 (d, 2H, J = 8.6 Hz), 7.88 (d, 2H, J = 8.6 Hz). FABMS m/z = 419 (m+H⁺). HRMS (calcd for C₂₀H₂₀FN₂O₅S 419.1077) 419.1082.

Example 142



4-[2-Ethyl-4-(3-fluorophenyl)-oxazol-5-yl]benzenesulfonamide

Step 1: Preparation of 1-(3-fluorophenyl)-2-phenyl-ethan-1-one

3-Fluorobenzaldehyde (10.0 g, 81 mmol), dichloromethane (100 mL), and zinc iodide (5 mg) were stirred at 0 °C under nitrogen. Trimethylsilylcyanide (8.83 g, 89 mmol) was added dropwise with a slight exotherm. The cooling bath was removed and the reaction proceeded for 2 hours when water (5 mL) was added dropwise. The mixture was washed with brine (2 X 30 mL), dried over magnesium sulfate, and concentrated under high vacuum. The resulting oily residue was dissolved in tetrahydrofuran (150 mL) and cooled to -78 °C under nitrogen. Lithium diisopropylamine (2.0 M solution in heptane/tetrahydrofuran/ethylbenzene, 45 mL, 90 mmol) was added dropwise maintaining the temperature below -60 °C.

The reaction was stirred for 1/2 hour and benzyl bromide was added (15.4 g, 90 mmol) all at once. The cooling bath was removed and the mixture was stirred until the temperature reached -15 °C and poured into a stirred solution of 1N hydrochloric acid (150 mL) and trifluoroacetic acid (10 mL). After one hour, the mixture was extracted with ethyl acetate (2 X 50 mL), combined, washed with brine (2 X 50 mL), and concentrated. The resulting dark oily residue was treated with 2.5 N sodium hydroxide, and a solid was collected by filtration. Recrystallization from ethanol/water resulted in 11.4 g of a light yellow solid: mp 54.6-57.0 °C. This material was used in the next step without further purification or characterization.

Step 2. Preparation of 1-(3-fluorophenyl)-2-bromo-2-phenyl-ethan-1-one

1-(3-Fluorophenyl)-2-phenyl-ethan-1-one (Step 1) (4.28 g, 20 mmol), acetic acid (50 mL), 33% hydrobromic acid in acetic acid (10 mL), and bromine (3.2 g, 20 mmol) were stirred at room temperature for 2 hours. The mixture was concentrated and ethyl acetate (150 mL) was added. After washing with brine, drying over magnesium sulfate, and concentrating, 5.3 g of a brown oil was obtained. This material was used in the next step without further purification or characterization.

Step 3. Preparation of 2-ethyl-4-(3-fluorophenyl)-5-phenyloxazole.

1-(3-Fluorophenyl)-2-bromo-2-phenyl-ethan-1-one (Step 2) (1.5 g, 5.15 mmol), N',N'-dimethylformamide (25 mL), sodium hydroxide (60%, 0.23 mL, 5.67 mmol), and propionic acid (0.33 g, 5.67 mmol) were stirred at room temperature overnight. After the addition of ethyl acetate (100 mL), the mixture was washed successively with 1N hydrochloric acid, brine, and water. The organic

214

solution was dried over magnesium sulfate and concentrated. The resulting oily residue was dissolved in acetic acid (50 mL) and ammonium acetate (6.0 g) was added. After refluxing for 12 hours, the mixture was concentrated, dissolved in ethyl acetate (100 mL), washed with brine, dried and concentrated. Purification by flash column chromatography (eluting with hexanes:ethyl acetate (20:1)) yielded 0.6 g of a light yellow oil which formed an oily solid upon standing: ^1H NMR (CDCl_3 /300 MHz) 7.57 (m, 2H), 7.5-7.25 (m, 5H), 7.02 (m, 1H), 2.88 (q, $J = 8.7$ Hz, 2H), 1.42 (t, $J = 8.7$ Hz, 3H). This material was used in the next step without further purification or characterization.

15 Step 4: Preparation of 4-[2-ethyl-4-(3-fluorophenyl)-oxazol-5-yl]benzenesulfonamide

Chlorosulfonic acid (10 mL) was cooled to -78°C . 2-Ethyl-4-(3-fluorophenyl)-5-phenyloxazole (Step 3) (0.6 g, 22 mmol) was dissolved in a minimum amount of dichloromethane and added dropwise. The mixture was stirred and warmed to room temperature over 5 hours, when it was added dropwise to ice (500 mL). Ammonium hydroxide (100 mL) and ethyl acetate (100 mL) were added and the mixture was stirred overnight. The layers were separated and the organic phase was washed with 1 N hydrochloric acid, and brine. After drying over magnesium sulfate and concentrating, 0.4 g of a light yellow solid was recrystallized from ethanol water: mp 133.5 - 135.1°C . ^1H NMR (acetone- d_6 /300 MHz) 7.96 (d, $J = 9.3$ Hz, 2H), 7.78 (d, $J = 9.3$ Hz, 2H), 7.5-7.3 (m, 3H), 7.18 (m, 1H), 6.70 (bs, 2H), 2.90 (q, $J = 8.3$ Hz, 2H), 1.40 (t, $J = 8.3$ Hz, 3H). FABHRMS m/z 347.0848. (M^+H , $\text{C}_{17}\text{H}_{15}\text{FN}_2\text{O}_3\text{S}$ calcd 347.0866).

35

BIOLOGICAL EVALUATION

Rat Carrageenan Foot Pad Edema Test

The carrageenan foot edema test was performed with materials, reagents and procedures essentially as described by Winter, et al., (*Proc. Soc. Exp. Biol. Med.*, 111, 544 (1962)). Male Sprague-Dawley rats were selected in each group so that the average body weight was as close as possible. Rats were fasted with free access to water for over sixteen hours prior to the test. The rats were dosed orally (1 mL) with compounds suspended in vehicle containing 0.5% methylcellulose and 0.025% surfactant, or with vehicle alone. One hour later a subplantar injection of 0.1 mL of 1% solution of carrageenan/sterile 0.9% saline was administered and the volume of the injected foot was measured with a displacement plethysmometer connected to a pressure transducer with a digital indicator. Three hours after the injection of the carrageenan, the volume of the foot was again measured. The average foot swelling in a group of drug-treated animals was compared with that of a group of placebo-treated animals and the percentage inhibition of edema was determined (Otterness and Bliven, Laboratory Models for Testing NSAIDs, in Non-steroidal Anti-Inflammatory Drugs, (J. Lombardino, ed. 1985)). The % inhibition shows the % decrease from control paw volume determined in this procedure and the data for selected compounds in this invention are summarized in Table 6.

Rat Carrageenan-induced Analgesia Test

The analgesia test using rat carrageenan was performed with materials, reagents and procedures essentially as described by Hargreaves, et al., (*Pain*, 32, 77 (1988)). Male Sprague-Dawley rats were treated as previously described for the Carrageenan Foot Pad Edema test. Three hours after the injection of the carrageenan, the rats were placed in a special plexiglass container with a transparent floor having a high

intensity lamp as a radiant heat source, positionable under the floor. After an initial twenty minute period, thermal stimulation was begun on either the injected foot or on the contralateral uninjected foot. A photoelectric cell turned off the lamp and timer when light was interrupted by paw withdrawal. The time until the rat withdraws its foot was then measured. The withdrawal latency in seconds was determined for the control and drug-treated groups, and percent inhibition of the hyperalgesic foot withdrawal determined. Results are shown in Table 6.

TABLE 6.

	RAT PAW EDEMA		ANALGESIA	
	% Inhibition		% Inhibition	
	@ 10mg/kg body weight		@ 20mg/kg body weight	
Example				
	1	41*		44
	3	30		-
20	7	24		-
	8	12		-
	10	18		-
	11	42		-
	16	26		-
25	28	2		-
	30	4		-
	31	5		-
	52	61 ¹		-
	55	37 ¹		-
30	70	46 ¹		-
	1 @ 30mg/kg body weight			
	* @ 20mg/kg body weight			

Evaluation of COX I and COX II activity *in vitro*.

35 The compounds of this invention exhibited inhibition *in vitro* of COX-2. The COX-2 inhibition activity of the

compounds of this invention illustrated in the Examples was determined by the following methods.

a. Preparation of recombinant COX baculoviruses

5 Recombinant COX-1 and COX-2 were prepared as described by Gierse et al, [*J. Biochem.*, 305, 479-84 (1995)]. A 2.0 kb fragment containing the coding region of either human or murine COX-1 or human or murine COX-2 was cloned into a BamHI site of the baculovirus transfer vector pVL1393 (Invitrogen) to generate the baculovirus transfer vectors for COX-1 and COX-2 in a manner similar to the method of D.R. O'Reilly et al (*Baculovirus Expression Vectors: A Laboratory Manual* (1992)).

10 Recombinant baculoviruses were isolated by transfecting 4 µg of baculovirus transfer vector DNA into SF9 insect cells (2×10^8) along with 200 ng of linearized baculovirus plasmid DNA by the calcium phosphate method. See M.D. Summers and G.E. Smith, *A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures*, Texas Agric. Exp. Station Bull. 1555 (1987). Recombinant viruses were purified by three rounds of plaque purification and high titer (10^7 - 10^8 pfu/ml) stocks of virus were prepared. For large scale production, SF9 insect cells were infected in 10 liter fermentors (0.5×10^6 /ml) with the recombinant baculovirus stock such that the multiplicity of infection was 0.1. After 72 hours the cells were centrifuged and the cell pellet homogenized in Tris/Sucrose (50 mM: 25%, pH 8.0) containing 1% 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate (CHAPS). The homogenate was centrifuged at 10,000xG for 30 minutes, and the resultant supernatant was stored at -80°C before being assayed for COX activity.

35 b. Assay for COX-1 and COX-2 activity

COX activity was assayed as PGE₂ formed/ μ g protein/time using an ELISA to detect the prostaglandin released. CHAPS-solubilized insect cell membranes containing the appropriate COX enzyme were incubated in a potassium phosphate buffer (50 mM, pH 8.0) containing epinephrine, phenol, and heme with the addition of arachidonic acid (10 μ M). Compounds were pre-incubated with the enzyme for 10-20 minutes prior to the addition of arachidonic acid. Any reaction between the arachidonic acid and the enzyme was stopped after ten minutes at 37°C/room temperature by transferring 40 μ l of reaction mix into 160 μ l ELISA buffer and 25 μ M indomethacin. The PGE₂ formed was measured by standard ELISA technology (Cayman Chemical). Results are shown in Table 7.

TABLE 7.

Example	COX-1	COX-2
	ID ₅₀ μ M	ID ₅₀ μ M
1	6.9	<0.1
3	>10	<0.1
14	>30	>10
15	>30	0.2
25	>10	0.5
28	>100	<0.1
30	>100	<0.1
31	>100	<0.1
32	15.9	<0.1
35	72	7.9
36	24.7	1.4
38	72	<0.1
39	>100	79
40	26	<0.1

TABLE 7. (cont)

Example	COX-1		COX-2	
	ID ₅₀	μ M	ID ₅₀	μ M
5	42	11.4	<0.1	
	51	14.0	<0.1	
	52	35	0.2	
	53	>100	0.5	
	58	31.0	<0.1	
10	67	33	0.8	
	69	79	0.5	
	70	>100	<0.1	
	71	51	0.1	
	72	>100	2.2	
15	73	47.5	<0.1	
	75	>100	<0.1	
	76	>100	2.7	
	77	18	<0.1	
	78	>100	2.8	
20	82	>100	0.5	
	83	33	1.6	
	85	>100	2.7	
	88	20.3	<0.1	
	89	>100	2.1	
25	91	>100	6.2	
	92	28.3	0.2	
	93	>100	11.2	
	94	17.5	0.1	
	95	>100	1.9	
30	96	17.5	0.1	
	100	>100	3.2	
	101	>100	3.0	
	103	11.3	<0.1	
	106	14.8	<0.1	
35	112	>100	2.7	
	113	>100	0.4	

TABLE 7. (cont)

Example	COX-1		COX-2	
	ID ₅₀ μ M		ID ₅₀ μ M	
5	115	>100	7.5	
	120	34	0.4	
	122	35.5	0.2	
	123	>100	1.5	
	124	>100	<0.1	
10	130	>100	7.7	
	131	>100	8.4	
	132	26.5	0.1	
	141	65.5	1.1	

15

Also embraced within this invention is a class of pharmaceutical compositions comprising the active compounds of this combination therapy in association with one or more non-toxic, pharmaceutically-acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. The active compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The active compounds and composition may, for example, be administered orally, intravascularly (IV), intraperitoneally, subcutaneously, intramuscularly (IM) or topically.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, hard or soft capsule, lozenges, dispensable powders, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules.

The active ingredient may also be administered by injection (IV, IM, subcutaneous or jet) as a composition wherein, for example, saline, dextrose, or water may be used as a suitable carrier. The pH of the composition may be adjusted, if necessary, with suitable acid, base, or buffer. Suitable bulking, dispersing, wetting or suspending agents, including mannitol and PEG 400, may also be included in the composition. A suitable parenteral composition can also include a compound formulated as a sterile solid substance, including lyophilized powder, in injection vials. Aqueous solution can be added to dissolve the compound prior to injection.

The amount of therapeutically active compounds that are administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the inflammation or inflammation related disorder, the route and frequency of administration, and the particular compound employed, and thus may vary widely. The prodrug compositions should include similar dosages as for the parent compounds. The pharmaceutical compositions may contain active ingredients in the range of about 0.1 to 1000 mg, preferably in the range of about 0.5 to 250 mg and most preferably between about 1 and 60 mg. A daily dose of about 0.01 to 100 mg/kg body weight, preferably between about 0.05 and about 20 mg/kg body weight and most preferably between about 0.1 to 10 mg/kg body weight, may be appropriate. The daily dose can be administered in one to four doses per day.

In the case of skin conditions, it may be preferable to apply a topical preparation of compounds of this invention to the affected area two to four times a day.

For disorders of the eye or other external tissues, e.g., mouth and skin, the formulations are preferably

applied as a topical gel, spray, ointment or cream, or as a suppository, containing the active ingredients in a total amount of, for example, 0.075 to 30% w/w, preferably 0.2 to 20% w/w and most preferably 0.4 to 15% w/w. When formulated in an ointment, the active ingredients may be employed with either paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example at least 30% w/w of a polyhydric alcohol such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol, polyethylene glycol and mixtures thereof. The topical formulation may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogs. The compounds of this invention can also be administered by a transdermal device. Preferably topical administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety. In either case, the active agent is delivered continuously from the reservoir or microcapsules through a membrane into the active agent permeable adhesive, which is in contact with the skin or mucosa of the recipient. If the active agent is absorbed through the skin, a controlled and predetermined flow of the active agent is administered to the recipient. In the case of microcapsules, the encapsulating agent may also function as the membrane. The transdermal patch may include the compound in a suitable solvent system with an adhesive system, such as an acrylic emulsion, and a polyester patch.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an

emulsifier. it may comprise a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make-up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations. Emulsifiers and emulsion stabilizers suitable for use in the formulation of the present invention include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate, and sodium lauryl sulfate, among others.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus, the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters may be used. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredients are dissolved or suspended in suitable carrier, especially an aqueous solvent for the active ingredients. The antiinflammatory active ingredients are

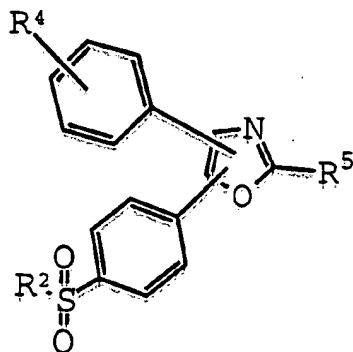
preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% and particularly about 1.5% w/w.

For therapeutic purposes, the active compounds of this combination invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered *per os*, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanolic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations.

What is claimed is:

1. A compound of Formula II



II

wherein R^2 is selected from lower alkyl and amino; wherein R^4 is selected from hydrido, alkyl, alkylamino, alkoxy and halo; and wherein R^5 is selected from halo, mercapto, carboxyalkylthio, carboxyalkylthioalkyl, carboxyalkoxy, carboxyalkoxyalkyl, haloalkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkoxy, aryloxy, alkylamino, aminocarbonyl, alkoxyalkyl, carboxy(haloalkyl), aminoalkyl, hydroxyalkoxyalkyl, alkylcarbonyl, phosphonylalkyl, alkylcarbonylaminoalkyl, aralkoxycarbonylaminoalkyl, amino acid residue, heterocyclalkyl, and cyanoalkyl; or a pharmaceutically-acceptable salt thereof.

2. Compound of Claim 1 wherein R^2 is selected from lower alkyl and amino; wherein R^4 is selected from hydrido, lower alkyl, lower alkylamino, lower alkoxy and halo; and wherein R^5 is selected from halo, mercapto, lower carboxyalkylthio, lower carboxyalkylthioalkyl, lower haloalkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, lower alkoxy, aryloxy, lower alkylamino, aminocarbonyl, lower alkoxyalkyl, lower carboxy(haloalkyl), lower aminoalkyl, lower hydroxyalkoxyalkyl, lower alkylcarbonyl, lower

phosphonylalkyl, lower alkylcarbonylaminoalkyl, lower aralkoxycarbonylaminoalkyl, amino acid residue, lower heterocyclylalkyl, and lower cyanoalkyl; or a pharmaceutically-acceptable salt thereof.

5

3. Compound of Claim 2 wherein R² is selected from methyl and amino; wherein R⁴ is selected from hydrido, methyl, ethyl, n-propyl, isopropyl, butyl, tert-butyl, isobutyl, amino, methoxy, ethoxy, propoxy, butoxy, N-methylamino, N,N-dimethylamino, fluoro, chloro, bromo and iodo; and wherein R⁵ is selected from chloro, fluoro, bromo, iodo, mercapto, carboxymethylthio, carboxyethylthio, carboxyethylthiomethyl, trifluoromethoxy, methylthio, ethylthio, methylsulfinyl, methylsulfonyl, methoxy, ethoxy, propoxy, butoxy, phenyloxy, benzyloxy, N-methylamino, N,N-dimethylamino, N,N-diethylamino, aminocarbonyl, methoxymethyl, α -bromocarboxymethyl, aminoethyl, bis(hydroxymethyl)methoxymethyl, methylcarbonyl, N-methylcarbonylaminomethyl, aminopropyl, pyrrolidinylmethyl, pyrrolidinyethyl, pyrrolylpropyl, pyrrolylethyl, methylcarbonylaminomethyl, N-(benzyloxycarbonyl)aminomethyl, N-(benzyloxycarbonyl)aminoethyl, N-(benzyloxycarbonyl)aminopropyl, N-methyl-N-(benzyloxycarbonyl)aminoethyl, [N-(phenylmethoxycarbonyl)amino]methoxycarbonylpropyl, [N-(phenylmethoxycarbonyl)amino]carboxypropyl, piperidinyethyl, tetrazolylpentyl, and cyanopentyl; or a pharmaceutically-acceptable salt thereof.

30

4. Compound of Claim 3 selected from compounds and their pharmaceutically-acceptable salts, of the group consisting of

35

phenylmethyl [2-[5-[4-(aminosulfonyl)phenyl]-4-phenyloxazol-2-yl]methyl]carbamate;

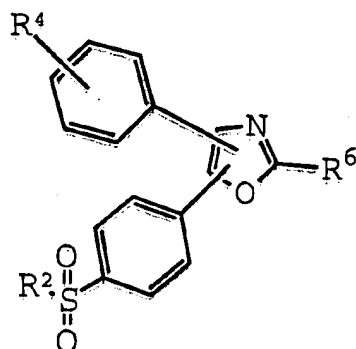
- phenylmethyl [2-[5-[4-(aminosulfonyl)phenyl]-4-phenyloxazol-2-yl]ethyl]carbamate;
- phenylmethyl [2-[5-[4-(aminosulfonyl)phenyl]-4-phenyloxazol-2-yl]ethyl]methylcarbamate;
- 5 phenylmethyl [2-[5-[4-(aminosulfonyl)phenyl]-4-phenyloxazol-2-yl]propyl]carbamate;
- methyl 5-[4-(aminosulfonyl)phenyl]- α R-[[(phenylmethoxy) carbonyl] aminno]-4-phenyloxazole-2-butanate;
- 10 5-[4-(aminosulfonyl)phenyl]- α R-[[(phenylmethoxy) carbonyl] aminno]-4-phenyloxazole-2-butanolic acid;
- 4-[2-cyanopentyl-4-phenyloxazol-5-yl]benzenesulfonamide;
- 4-[2-methoxymethyl-4-phenyl-5-oxazolyl]benzenesulfonamide;
- 15 [5-[(4-aminosulfonyl)phenyl]-4-phenyl-oxazol-2-yl]propanamine;
- 4-[2-(1-pyrrolyl)propyl-4-phenyloxazol-5-yl]benzenesulfonamide;
- 20 [5-[(4-aminosulfonyl)phenyl]-4-phenyl-oxazol-2-yl]ethanamine;
- 4-[2-(1-piperidiny)ethyl-4-phenyloxazol-5-yl]benzenesulfonamide;
- 4-[2-(1-pyrrolidinyl)methyl-4-phenyloxazol-5-yl]benzenesulfonamide;
- 25 4-[2-[bis(hydroxymethyl)methoxy]methyl-4-phenyloxazol-5-yl]benzenesulfonamide;
- 2-[5-[(4-aminosulfonyl)phenyl]-4-phenyloxazol-2-yl]ethan-2-one;
- 30 4-[2-chloro-4-phenyl-5-oxazolyl]benzenesulfonamide;
- 4-[2-mercapto-4-phenyl-5-oxazolyl]benzenesulfonamide;
- 4-[2-(3-chlorophenoxy)-4-phenyl-5-(oxazolyl)]benzenesulfonamide;
- 5-(4-aminosulfonylphenyl)-4-phenyl-2-oxazolyl]mercaptoacetic acid;
- 35 4-[4-phenyl-2-(2,2,2-trifluoroethoxy-5-oxazolyl)]benzenesulfonamide;

- 4-[2-(methylthio)-4-phenyl-5-oxazolyl]benzenesulfonamide;
4-[2-methylsulfinyl)-4-phenyl-5-oxazolyl]benzenesulfonamide;
5 4-[2-(methylsulfonyl)-4-phenyl-5-oxazolyl]benzenesulfonamide;
4-[2-(2,3,4,5,6-pentafluorophenoxy)-4-phenyl-5-oxazolyl]benzenesulfonamide;
4-[2-methoxy-4-phenyl-5-oxazolyl]benzenesulfonamide;
10 ethyl 2-[[5-(4-aminosulfonylphenyl)-4-phenyl-2-oxazolyl]oxy]benzoate;
ethyl 3-[[5-(4-aminosulfonylphenyl)-4-phenyl-2-oxazolyl]oxy]benzoate;
4-[2-(N,N-dimethylamino)-4-phenyl-5-oxazolyl]benzenesulfonamide;
15 4-methyl-3-[5-phenyl-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide;
4-[4-(3-aminosulfonyl-4-methylphenyl)-2-trifluoromethyl-5-oxazolyl]benzenesulfonamide;
20 4-methyl-3-[4-phenyl-2-trifluoromethyl-5-oxazolyl]benzenesulfonamide;
4-[4-aminosulfonylphenyl)-5-(3-fluoro-4-methoxyphenyl)-2-oxazolyl]α-bromoacetic acid;
4-[4-(3-aminosulfonyl-5-fluoro-4-methoxyphenyl)-2-trifluoromethyl-5-oxazolyl]benzenesulfonamide;
25 5-fluoro-4-methoxy-3-[5-phenyl-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide;
ethyl 4-[[5-(4-aminosulfonylphenyl)-4-phenyl-2-oxazolyl]oxy]benzoate;
30 4-[5-(4-bromophenyl)-2-methoxymethyl-4-oxazolyl]benzenesulfonamide;
4-[2-methoxymethyl-5-phenyl-4-oxazolyl]benzenesulfonamide;
4-[4-(4-chlorophenyl)-2-methoxymethyl-5-oxazolyl]benzenesulfonamide;
35 4-[4-(3-chlorophenyl)-2-methoxymethyl-5-oxazolyl]benzenesulfonamide;

- 4-[5-(4-chlorophenyl)-2-methoxymethyl-4-oxazolyl]benzenesulfonamide;
 4-[5-(3-chlorophenyl)-2-methoxymethyl-4-oxazolyl]benzenesulfonamide;
 5 4-[5-(4-fluorophenyl)-2-methoxymethyl-4-oxazolyl]benzenesulfonamide;
 4-[4-phenyl-2-(methylcarbonylaminoethyl)-5-oxazolyl]benzenesulfonamide;
 (R) 4-[4-phenyl-2-[2-(1-pyrrolyl)ethyl]-5-oxazolyl]benzenesulfonamide; and
 10 (S) 4-[4-phenyl-2-[2-(1-pyrrolyl)ethyl]-5-oxazolyl]benzenesulfonamide.

5. A compound of Formula III

15



III

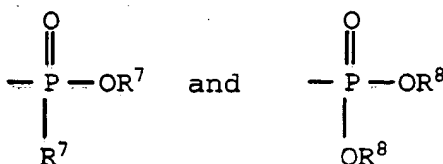
- wherein R^2 is selected from lower alkyl and amino;
 wherein R^4 is selected from hydrido, lower alkyl, lower
 20 alkylamino, lower alkoxy and halo; wherein R^6 is -Y-Q;
 wherein Y is selected from aryl, heterocyclyl,
 alkoxyalkyl, aryloxyalkyl, alkylaryloxyalkyl,
 aralkoxyalkyl, alkylaralkoxyalkyl, aminoalkyl,
 heterocyclylalkyl, alkylheterocyclyl,
 25 alkylheterocyclylalkyl, alkylaralkyl, aralkyl,
 alkynylaralkyl, alkyl, alkylsulfonylalkyl,
 alkylthioalkyl, and alkylsulfonylaminoalkyl; and
 wherein Q is an acidic moiety selected from carboxylic
 acid, tetrazole, phosphorous-containing acids, sulfur-
 30 containing acids, and the amide, ester and salt

derivatives of said acids; provided Y is not methyl when Q is $-P(O)(OH)_2$; and further provided Y is not methyl or ethyl when Q is carboxyl; or a pharmaceutically-acceptable salt thereof.

5

6. Compound of Claim 5 wherein R^2 is selected from lower alkyl and amino; wherein R^4 is selected from hydrido, lower alkyl, lower alkoxy and halo; wherein Y is selected from phenyl, five and six membered heterocyclyl, lower alkoxyalkyl, lower aminoalkyl, lower heterocyclylalkyl, lower alkylheterocyclyl, lower alkylheterocyclylalkyl, lower aryloxyalkyl, lower alkylaryloxyalkyl, lower aralkoxyalkyl, lower alkylaralkoxyalkyl, lower alkylaralkyl, lower alkynylaralkyl, lower aralkyl, lower alkylsulfonylalkyl, lower alkylthioalkyl, alkyl, and lower alkylsulfonylaminoalkyl; wherein Q is selected from carboxyl, lower alkoxycarbonyl, lower aralkoxycarbonyl, tetrazolyl,

20

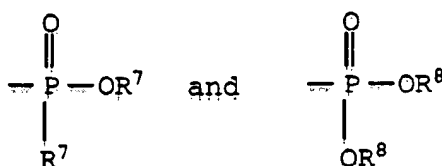


25

and wherein each of R^7 and R^8 is independently selected from hydrido, lower alkyl, lower cycloalkyl, phenyl and lower aralkyl; or a pharmaceutically-acceptable salt thereof.

7. Compound of Claim 6 wherein R^2 is selected from methyl and amino; wherein R^4 is selected from hydrido, methyl, methoxy, fluoro, chloro and bromo; wherein Y is selected from phenyl, pyridyl, pyrrolyl, pyrrolidinyl, imidazolyl, piperidinyl, methoxymethyl, 3-aminopropyl, pyrrolylmethyl, pyrrolidinylmethyl, pyrrolylpropyl, methylpyrrolyl, ethylphenylmethyl, methylphenylethyl, phenoxymethyl, methylphenoxymethyl, benzyl, ethylsulfonylmethyl, ethylthiomethyl, methylthiomethyl,

- methylthioethyl, methyl, ethyl, propyl, pentyl, 2,2-dimethylpropyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-methylpropyl, butyl, and methylsulfonylaminopropyl; wherein Q is selected from carboxyl, methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, benzyloxycarbonyl, tetrazolyl,



- and wherein each of R^7 and R^8 is independently selected from hydrido, methyl, and ethyl; or a pharmaceutically-acceptable salt thereof.

8. Compound of Claim 7 selected from compounds and their pharmaceutically-acceptable salts, of the group consisting of

- 5-[(4-aminosulfonyl)phenyl]-4-phenyloxazole-2-pentanoic acid;
methyl 5-[(4-aminosulfonyl)phenyl]-4-phenyloxazole-2-pentanoate;
methyl 5-[(4-aminosulfonyl)phenyl]-4-phenyloxazole-2-butanoate;
5-[(4-aminosulfonyl)phenyl]-4-phenyloxazole-2-butanoic acid;
3-[[[5-[(4-aminosulfonyl)phenyl]-4-phenyloxazol-2-yl]methyl]oxy]acetic acid;
5-[(4-aminosulfonyl)phenyl]-4-phenyl- β,β -dimethyloxazole-2-butanoic acid;
methyl 5-[(4-aminosulfonyl)phenyl]-4-phenyloxazole-2-hexanoate;
5-[(4-aminosulfonyl)phenyl]-4-phenyloxazole-2-hexanoic acid;
diethyl [[5-[(4-aminosulfonyl)phenyl]-4-phenyloxazole-2-yl]propyl]phosphonate;

- [[5-[(4-aminosulfonyl)phenyl]-4-phenyloxazole-2-yl]propyl]phosphonic acid;
diethyl [[5-[(4-aminosulfonyl)phenyl]-4-phenyloxazole-2-yl]methyl]phosphonate;
5 ethyl [[5-[(4-aminosulfonyl)phenyl]-4-phenyloxazole-2-yl]methyl]phosphonate;
3-[[[5-[4-aminosulfonyl]phenyl]-4-phenyloxazol-2-yl]methyl]sulfonyl]propanoic acid;
methyl 3-[[[5-[4-aminosulfonyl]phenyl]-4-phenyloxazol-2-yl]ethyl]thio]acetate;
10 3-[[[5-[4-aminosulfonyl]phenyl]-4-phenyloxazol-2-yl]ethyl]thio]acetic acid;
tert-butyl 3-[[[5-[4-aminosulfonyl]phenyl]-4-phenyloxazol-2-yl]methyl]thio]acetate;
15 3-[[[5-[4-aminosulfonyl]phenyl]-4-phenyloxazol-2-yl]methyl]thio]acetic acid;
5-[(4-aminosulfonyl)phenyl]-4-phenyl- β -methyloxazole-2-butanoic acid;
methyl 5-[(4-aminosulfonyl)phenyl]-4-phenyl- β -methyloxazole-2-butanate;
20 4-[(2-tetrazolyl)pentyl]-4-phenyloxazol-5-yl]benzenesulfonamide;
[[[5-[(4-aminosulfonyl)phenyl]-4-phenyloxazol-2-yl]methyl]-1-pyrrol-2-yl]carboxylic acid;
25 methyl [[[5-[(4-aminosulfonyl)phenyl]-4-phenyloxazol-2-yl]methyl]-1-pyrrol-2-yl]carboxylate;
[[[5-[(4-aminosulfonyl)phenyl]-4-phenyloxazol-2-yl]-2-pyrrol-1-yl]acetic acid;
ethyl [[[5-[(4-aminosulfonyl)phenyl]-4-phenyloxazol-2-yl]-2-pyrrol-1-yl]acetate;
30 methyl [[[5-[(4-aminosulfonyl)phenyl]-4-phenyloxazol-2-yl]methyl]-1-pyrrolidin-2-yl]carboxylate;
methyl [[[5-[(4-aminosulfonyl)phenyl]-4-phenyloxazol-2-yl]propyl]aminosulfonyl]acetate;
35 5-[(4-aminosulfonyl)phenyl]-4-phenyl- β S-amino-oxazole-2-butanoic acid;
methyl [5-[(4-aminosulfonyl)phenyl]-4-(3,4-dichlorophenyl)oxazole]-2-propanoate;

- 5-[(4-aminosulfonyl)phenyl]-4-(3,4-dichlorophenyl)oxazole-2-propanoic acid;
methyl 5-[(4-aminosulfonyl)phenyl]-4-(3,4-dichlorophenyl)oxazole-2-butanoate;
- 5 5-[(4-aminosulfonyl)phenyl]-4-(3,4-dichlorophenyl)oxazole-2-butanoic acid;
methyl 5-[(4-aminosulfonyl)phenyl]-4-(3,4-dichlorophenyl)oxazole-2-pentanoate;
- 10 5-[(4-aminosulfonyl)phenyl]-4-(3,4-dichlorophenyl)oxazole-2-pentanoic acid;
- 4-[(4-aminosulfonyl)phenyl]-5-(4-fluorophenyl)oxazole-2-pentanoic acid;
methyl 4-[(4-aminosulfonyl)phenyl]-5-(4-fluorophenyl)oxazole-2-pentanoate;
- 15 5-[(4-aminosulfonyl)phenyl]-4-(3,4-dichlorophenyl)- β,β -dimethyloxazole-2-butanoic acid;
methyl 5-[(4-aminosulfonyl)phenyl]-4-(3,4-dichlorophenyl)- β,β -dimethyloxazole-2-butanoate;
- 20 4-[(4-methylsulfonyl)phenyl]-5-(3,4-dichlorophenyl)oxazole-2-butanoic acid;
methyl 4-[(4-methylsulfonyl)phenyl]-5-(3,4-dichlorophenyl)oxazole-2-butanoate;
- 4-[(4-aminosulfonyl)phenyl]-5-(3,4-dichlorophenyl)oxazole-2-butanoic acid;
- 25 methyl 4-[(4-aminosulfonyl)phenyl]-5-(3,4-dichlorophenyl)oxazole-2-butanoate;
- 5-[(4-aminosulfonyl)phenyl]-4-phenyl- α S-(1H-pyrrol-1-yl)oxazole-2-butanoic acid;
- 30 methyl 5-[(4-aminosulfonyl)phenyl]-4-phenyl- α S-(1H-pyrrol-1-yl)oxazole-2-butanoate;
- 3-[[[5-[(4-aminosulfonyl)phenyl]-4-phenyloxazol-2-yl]methyl]thio]propanoic acid;
- 3-[[[4-[(4-aminosulfonyl)phenyl]-5-phenyloxazol-2-yl]methyl]thio]propanoic acid;
- 35 tert butyl 3-[[[5-[(4-aminosulfonyl)phenyl]-4-phenyloxazol-2-yl]methyl]thio]propanoate;

tert butyl 3-[[[4-[4-aminosulfonyl)phenyl]-5-phenyloxazol-2-yl)methyl]thio]propanoate;
 4-[2-[5-[(4-aminosulfonyl)phenyl]-4-phenyl-oxazol-2-yl)methyl]phenylpropanoic acid;
 5 methyl 4-[2-[5-[(4-aminosulfonyl)phenyl]-4-phenyl-oxazol-2-yl)methyl]phenylpropynoic acid;
 methyl 5-[(4-aminosulfonyl)phenyl]-4-(4-fluorophenyl)oxazole-2-pentanoate; and
 5-[4-(aminosulfonyl)phenyl]-4-(4-fluorophenyl)oxazole-2-pentanoic acid.

9. A Compound selected from compounds and their pharmaceutically-acceptable salts, of the group consisting of

4-[2-[[4-[3-(hydroxy)-1-propynyl]phenyl)methyl]-4-phenyloxazol-5-yl]benzenesulfonamide;
 4-[2-[[4-[3-(N,N-dimethylamino)-1-propynyl]phenyl)methyl]-4-phenyloxazol-5-yl]benzenesulfonamide;
 4-[2-[[4-[3-(N,N-dimethylamino)propyl]phenyl)methyl]-4-phenyloxazol-5-yl]benzenesulfonamide;
 4-[2-[[4-[3-(2-methyl-1H-imidazol-1-yl)-1-propynyl]phenyl)methyl]-4-phenyloxazol-5-yl]benzenesulfonamide;
 1,1-dimethylethyl [3-[4-[[5-[4-(aminosulfonyl)phenyl]-4-phenyloxazol-2-yl)methyl]phenyl]-2-propynyl]carbamate;
 4-[2-[[4-[3-(2-methyl-1H-imidazol-1-yl)-1-propyl]phenyl)methyl]-4-phenyloxazol-5-yl]benzenesulfonamide;
 4-[2-[[4-[3-(amino)-1-propynyl]phenyl)methyl]-4-phenyloxazol-5-yl]benzenesulfonamide;
 4-[2-[[4-[3-(tert-butylamino)-1-propynyl]phenyl)methyl]-4-phenyloxazol-5-yl]benzenesulfonamide;
 4-phenyl-2-(benzyloxymethyl)-5-(4-methylsulfonylphenyl)oxazole;

- 5-phenyl-2-(benzyloxymethyl)-4-(4-methylsulfonylphenyl)oxazole;
4-[4-phenyl-2-(2-pyrrolyl)-5-oxazolyl]benzenesulfonamide;
5 4-[2-ethyl-4-(3-fluorophenyl)oxazol-5-yl]benzenesulfonamide;
[5-[(4-aminosulfonyl)phenyl]-4-phenyl-oxazol-2-yl]ethyne;
4-[2-propargyl-4-phenyloxazol-5-yl]benzenesulfonamide;
10 4-(2-ethenyl)-4-phenyl-oxazol-5-yl]benzenesulfonamide;
ethyl [4-(4-aminosulfonylphenyl)-5-(3-fluoro-4-methoxyphenyl)]-2-oxazoleacetate;
[4-(4-aminosulfonylphenyl)-5-cyclohexyl]-2-oxazoleacetic acid;
15 [5-(4-aminosulfonylphenyl)-4-(4-chlorophenyl)]-2-oxazoleacetic acid;
[4-(4-aminosulfonylphenyl)-5-(4-chlorophenyl)]-2-oxazoleacetic acid;
[4-(4-aminosulfonylphenyl)-5-(3-chloro-4-fluorophenyl)]-2-oxazoleacetic acid;
20 [4-(4-aminosulfonylphenyl)-5-(3,4-dichlorophenyl)]-2-oxazoleacetic acid;
[4-(4-aminosulfonylphenyl)-5-(3,4-difluorophenyl)]-2-oxazoleacetic acid;
25 [5-(3,4-difluorophenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide;
[5-(4-aminosulfonylphenyl)-4-phenyl]-2-oxazolepropionic acid;
4-[4-phenyl-5-oxazolyl]benzenesulfonamide;
30 4-[5-(4-chlorophenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide;
4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide;
4-[4-(N,N-dimethylamino)phenyl-2-trifluoromethyl-5-oxazolyl]benzenesulfonamide;
35 [4-(4-aminosulfonylphenyl)-5-(3-fluoro-4-methoxyphenyl)]-2-oxazoleacetic acid;

- 4-(4-methylphenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethyloxazole;
- 4-[5-(3-fluoro-4-methoxyphenyl)-2-methyl-4-oxazolyl]benzenesulfonamide;
- 5 5-(3-fluoro-4-methoxyphenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethyloxazole;
- 4-[5-(3-bromo-4-methoxy-5-fluorophenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide;
- 4-(4-fluorophenyl)-2-cyclohexyl-5-[4-(methylsulfonyl)phenyl]oxazole;
- 10 5-(4-fluorophenyl)-2-phenyl-4-[4-(methylsulfonyl)phenyl]oxazole;
- [5-(3,4-dichlorophenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide;
- 15 4-(3-fluoro-4-methoxyphenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethyloxazole;
- 4-[4-(4-bromophenyl)-2-methyl-5-oxazolyl]benzenesulfonamide;
- 4-[4-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl-5-oxazolyl]benzenesulfonamide;
- 20 4-[5-(3-chloro-4-fluorophenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide;
- 4-[5-(3-chloro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide;
- 25 4-[4-phenyl-2-(2-pyrrolyl)-5-oxazolyl]benzenesulfonamide;
- 4-[5-phenyl-2-difluoromethyl-4-oxazolyl]benzenesulfonamide;
- [5-phenyl-4-(aminosulfonylphenyl)-2-oxazolyl]methanol;
- 30 [4-phenyl-5-(aminosulfonylphenyl)-2-oxazolyl]methanol;
- [5-phenyl-4-(methylsulfonylphenyl)-2-oxazolyl]methanol;
- [4-phenyl-5-(methylsulfonylphenyl)-2-oxazolyl]methanol;
- [4-(3-fluoro-4-methoxyphenyl)-5-(aminosulfonylphenyl)-2-oxazolyl]methanol;
- 35 4-[5-phenyl-2-methyl-4-oxazolyl]benzenesulfonamide;
- 4-[5-(4-bromophenyl)-2-methyl-4-oxazolyl]benzenesulfonamide;
- [5-(aminosulfonylphenyl)-4-phenyl-2-oxazolyl]-2-ethanol;

- [5-(aminosulfonylphenyl)-4-phenyl-2-oxazolyl]-1-ethanol;
 4-[4-(3-fluorophenyl)-2-methyl-5-oxazolyl]benzenesulfonamide;
 4-[4-(4-chlorophenyl)-2-methyl-5-oxazolyl]benzenesulfonamide;
 5 [4-(phenyl)-5-(aminosulfonylphenyl)-2-oxazolyl]- α,α -dimethylmethanol;
 4-[4-(4-fluorophenyl)-2-methyl-5-oxazolyl]benzenesulfonamide;
 10 4-[4-(3-chlorophenyl)-2-ethyl-5-oxazolyl]benzenesulfonamide;
 [4-(3-chlorophenyl)-5-(aminosulfonylphenyl)-2-oxazolyl]-2-methanol;
 [4-(4-chlorophenyl)-5-(aminosulfonylphenyl)-2-oxazolyl]-2-methanol;
 15 4-[5-(3-chlorophenyl)-2-ethyl-4-oxazolyl]benzenesulfonamide;
 4-[4-phenyl-2-(1-methyl-2-pyrrolyl)-5-oxazolyl]benzenesulfonamide;
 20 4-[5-(4-chlorophenyl)-2-methyl-4-oxazolyl]benzenesulfonamide;
 4-[4-(3,4-dichlorophenyl)-2-ethyl-5-oxazolyl]benzenesulfonamide;
 [4-(3-chlorophenyl)-5-(aminosulfonylphenyl)-2-oxazolyl]- α,α -dimethylmethanol;
 25 [5-(3-chlorophenyl)-4-(aminosulfonylphenyl)-2-oxazolyl]- α,α -dimethylmethanol; and
 [4-(phenyl)-5-(aminosulfonylphenyl)-2-oxazolyl]-2-propanol.

30

10. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compound selected from a family of compounds of Claim 1, 2, 3, 4, 5, 6, 7, 8 or 9; or a pharmaceutically-acceptable salt thereof.

35

11. A method of treating inflammation or an inflammation-associated disorder in a subject, said

method comprising treating the subject having or
susceptible to said disorder with a therapeutically-
effective amount of a compound of Claim 1, 2, 3, 4,
5, 6, 7, 8 or 9; or a pharmaceutically-acceptable
5 salt thereof.

12. The method of Claim 11 for use in treatment of
inflammation.

10 13. The method of Claim 11 for use in treatment of
an inflammation-associated disorder.

14. The method of Claim 13 wherein the
inflammation-associated disorder is arthritis.

15

15. The method of Claim 13 wherein the
inflammation-associated disorder is pain.

16. The method of Claim 13 wherein the
20 inflammation-associated disorder is fever.

INTERNATIONAL SEARCH REPORT

Intern: al Application No

PCT/US 96/06992

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D263/32 A61K31/42 C07D413/06 C07D413/10 C07D263/34
C07D263/38 C07D263/46 C07D263/48 C07F9/653

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,94 27980 (SEARLE & CO) 8 December 1994 cited in the application see claims	1-8, 10-16
A	--- JOURNAL OF THE CHEMICAL SOCIETY, 1963, LETCHWORTH GB, pages 1363-1370, XP002009304 T.VAN ES ET AL: "Substitution of 4,5-diphenyl-oxazoles and -imidazoles, and some related compounds" cited in the application see the whole document	1-16
A	--- EP,A,0 517 590 (BELLON LABOR SA ROGER) 9 December 1992 see claims --- -/--	1-16

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search

25 July 1996

Date of mailing of the international search report

31. 07. 96

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+ 31-70) 340-3016

Authorized officer

Henry, J

INTERNATIONAL SEARCH REPORT

Intern al Application No

PCT/US 96/06992

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,91 19714 (BELLON LABOR SA ROGER) 26 December 1991 see claims	1-16
A	US,A,3 901 908 (FITZI KONRAD ET AL) 26 August 1975 cited in the application see column 5 ,line 36-column 6 ,line 4 see column 19, line 30 - column 19, line 35 -----	1-16

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 96/ 06992

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 11-16 are directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the compounds.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Intern. al Application No

PCT/US 96/06992

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9427980	08-12-94	US-A- 5380738 AU-B- 6949594 EP-A- 0699192	10-01-95 20-12-94 06-03-96
EP-A-0517590	09-12-92	FR-A- 2677355 AU-B- 1899192 WO-A- 9221664	11-12-92 08-01-93 10-12-92
WO-A-9119714	26-12-91	FR-A- 2663331 AT-T- 110381 AU-B- 8058391 CA-A- 2080340 DE-D- 69103630 DE-T- 69103630 EP-A- 0533827 ES-T- 2063513 US-A- 5403852	20-12-91 15-09-94 07-01-92 15-12-91 29-09-94 12-01-95 31-03-93 01-01-95 04-04-95
US-A-3901908	26-08-75	NONE	